

THE QUARTERLY JOURNAL OF MEDICINE

6133-56

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NEW SERIES, VOLUME VI
(VOLUME XXX OF THE CONTINUOUS SERIES)

1937

15320
OXFORD: AT THE CLARENDON PRESS

LONDON, EDINBURGH, NEW YORK, TORONTO AND MELBOURNE: HUMPHREY MILFORD

OXFORD UNIVERSITY PRESS
AMEN HOUSE, E.C. 4
LONDON EDINBURGH GLASGOW NEW YORK
TORONTO MELBOURNE CAPE TOWN BOMBAY
CALCUTTA MADRAS
HUMPHREY MILFORD
PUBLISHER TO THE UNIVERSITY

PRINTED IN GREAT BRITAIN AT THE UNIVERSITY PRESS, OXFORD
BY JOHN JOHNSON, PRINTER TO THE UNIVERSITY

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CORRIGENDA

PAGES 310 and 311

All the temperatures of Case 14, W. M. were below 37.5 and the last 5 pulse-rates were below 80.

PAGE 319

25. Günther, H., *ibid.*, 1920, cxxxiv. 275.

should read

25. Günther, H., *ibid.*, 1920, cxxxiv. 257.

31. Kämmerer, H., and Weisbecker, H. *Arch. f. exper. Path. u. Pharm.*, Berl., 1926, iii. 263.

should read

31. Kämmerer, H., and Weisbecker, H., *Arch. f. exper. Path. u. Pharm.*, Berl., 1926, cxi. 263.

43. Shibuya, H., *Strahlentherapie*, 1924, 710.

should read

43. Shibuya, H., *Strahlentherapie*, 1924, xviii. 710.

A STUDY OF THE CHOLINE ESTERASE ACTIVITY IN NERVOUS AND MENTAL DISORDERS¹

BY HENRY TOD AND M. S. JONES
(From the Royal Edinburgh Hospital)

In a previous paper, Jones and Tod (1), a method was described measuring the C.E. (choline esterase) activity of blood serum. The present investigation has been carried out on 203 cases of psychotic and neurotic material. The distribution of the cases was as follows: Anxiety neurosis—27 cases; hysteria—15 cases; involuntional melancholia—36 cases; manic-depressive insanity, depressive phase—43 cases; manic phase—18 cases; schizophrenia—24 cases; catatonic stupors—6 cases; paranoia and paraphrenia—14 cases; epilepsy and hystero-epilepsy—10 cases; and thyrotoxic states—10 cases.

The C.E. unit is the number of μ l. of CO_2 evolved by one ml. of serum in one minute at 760 mm. Hg pressure and 37°C . Thirty normal controls were investigated and gave figures ranging from 53 units to 114 units with a mean of 83 units. The results obtained in the psychotic and neurotic cases have been examined statistically, comparing in each case the mean in the particular condition with the normal mean by Fisher's 't' method. The value of P is the probability that a difference such as that observed would be found on the assumption that the two groups (that under examination and the normal) were equivalent. A value of P less than 0.05 is commonly considered to indicate a significant difference.

The results were as follows:—

Anxiety states (27 cases)—Range 56 to 176; Mean 103; $P < 0.01$, 40 estimations.
Catatonic stupor (6 cases)—Range 26 to 58; Mean 46; $P < 0.01$, 8 estimations.
Epilepsy (10 cases)—Range 44 to 116; Mean 65; $P < 0.01$, 16 estimations.
Schizophrenia (24 cases)—Range 48 to 114; Mean 76; P between 0.05 and 0.02, 33 estimations.

The above results for anxiety neurosis, catatonic stupor, and epilepsy are definitely significant, while that for schizophrenia is just significant.

Hysteria (15 cases)—Range 53 to 96; Mean 77; P between 0.2 and 0.1, 17 estimations.

Involuntional melancholia (36 cases)—Range 26 to 123; Mean 79; P between 0.3 and 0.2, 64 estimations.

Melancholia (43 cases)—Range 53 to 118; Mean 78; P between 0.2 and 0.1, 49 estimations.

Mania (18 cases)—Range 53 to 118; Mean 79; P between 0.4 and 0.3, 22 estimations.

¹ Received August 23, 1936.

Paranoia and paraphrenia (14 cases)—Range 53 to 115; Mean 82; P between 0.9 and 0.8, 14 estimations.

Thyrotoxic states (10 cases)—Range 63 to 142; Mean 95; P between 0.1 and 0.05, 10 estimations.

In none of the disorders in the second group is the variation significantly different from the normal.

Discussion

There is at the present moment no certainty as to the exact significance of the choline esterase level in the blood. The theory of chemical transmission of nervous impulses implies that acetyl-choline is evolved at the synapses of the neurones, and the acetyl-choline produced is undoubtedly depotentiated almost immediately by the choline esterase, which splits the acetyl-choline into acetic acid and relatively inactive choline.

Whether an increased production of acetyl-choline stimulates the body to produce more esterase to cope with the acetyl-choline is a point which is not yet settled. It is possible to conceive of a high esterase level indicating either a very active autonomic nervous system, with a high production of the transmitter acetyl-choline, or, conversely, indicating a diminished autonomic activity due to the more rapid destruction of acetyl-choline by the excess of esterase present. We are inclined to believe that the former hypothesis is correct.

The analysis of the esterase levels in the case material under discussion indicates that three groups are significant. On the one hand, there are the high values obtained with the anxiety states, and on the other, there are the low values obtained with the catatonic stupors and the epileptics. The obvious somatic evidences of autonomic over-activity in the anxiety states suggests an increased output of acetyl-choline, and a rise in the esterase level to combat this. The very low figures in catatonia may indicate the opposite extreme, where metabolism is reduced to a minimum and the involuntary nervous system is in a state of relative inactivity. Further, the complete immobility found in these cases may be another factor, as it is thought that acetyl-choline may be the chemical transmitter of the whole central nervous system, as well as of the autonomic nervous system.

Finally, anxiety and catatonia represent extremes, when judged from a purely emotional standpoint; and in this connexion may be mentioned the work of Dikshit (2) and Barsoum (3), who found that the acetyl-choline equivalent of extracts of basal ganglia was higher than in any other part of the central nervous system.

When one comes to consider the other groups, the subject becomes even more complex and we do not feel justified in putting any interpretation on the findings. It is obvious, however, that the schizophrenic group, as a whole, represents a degree of psychic dissociation, which, though not so marked as in the catatonic group, is nevertheless of a similar type.

Summary

1. An investigation has been made of choline esterase activity in the blood serum of 203 cases of psychotic and neurotic material.

2. Examining the results statistically a significant rise was found in anxiety states, and a significant fall in catatonic stupors and in cases of epilepsy.

3. The possible significance of these results is discussed.

The authors wish to express their thanks to Professor D. K. Henderson for facilities for carrying out this work and to the Medical Research Council for a personal grant to one of them (H. T.).

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1. Jones, M. S., and Tod, H., *Biochem. Journ.*, Cambridge, 1935, xxix. 2242.
2. Dikshit, B. B., *Journ. Physiol.*, Cambridge, 1934, lxxx. 409.
3. Barsoum, G. S., *ibid.*, 1935, lxxxiv. 259.



THE FATE OF LARGE DOSES OF IRON ADMINISTERED BY MOUTH¹

BY JOHN FLEMING BROCK AND DONALD HUNTER

(From the British Postgraduate Medical School and the London Hospital)

ALTHOUGH iron in large doses is widely used in the treatment of certain types of anaemia, we still have very little knowledge of what proportion of the iron which goes in at the mouth is excreted in the faeces and what proportion is retained by the body.

At the end of the last century Bunge claimed that no iron was retained at all when it was administered in the inorganic forms. We know now that Bunge was wrong, but our evidence is mostly derived by indirect methods or from animal experiments.

The indirect evidence depends on the assumption that a certain group of anaemias commonly referred to as the iron deficiency anaemias are in fact due mainly, if not entirely, to deficiency of iron in the body, and that the recovery of the anaemia can be regarded as a measure of the amount of iron which is retained by the body when iron preparations are given by mouth. This indirect evidence has led to the conclusion that when doses of iron, such as 90 grains per day of iron and ammonium citrate or Bland's pill, are given by mouth the percentage retention of the iron by the body is very small.

It is the purpose of the present communication to show that when the retention of orally administered iron is directly studied by balance experiments, it is found that quite large amounts of iron are retained.

Plan of Experiments

Ten iron balance experiments were performed on nine patients. Five of these experiments were designed to measure also the effect of large doses of iron on the metabolism of calcium and phosphorus. In these experiments the patients were kept on a constant diet, and the intake and output of the three substances was measured in three-day periods. The details of one case are given in Table I. The experiment was divided into three stages—before, during, and after the administration of iron, each stage consisting of three or four periods.

The iron excretion figure for period 7 in Table I shows that there is a lag

¹ Received August 1, 1936.

in the excretion of the unabsorbed iron. For this reason the true measure of the retention of the iron administered during periods 4, 5, and 6 is the difference between the intake and output of iron in periods 4, 5, 6, and 7. This difficulty has been overlooked in some published accounts of iron balance studies, and may lead to fallaciously high rates of retention.

A further five experiments were performed with the sole object of measuring the retention of iron. In these experiments the cases, instead of being put upon a fixed diet, were allowed the ordinary ward diet, since small variations in its iron content from day to day are negligible compared with the large amount of iron given medicinally. The details of one case from this series are given in Table II, and show the method of calculating retention. Sufficient time was always allowed after the cessation of iron therapy for the iron excretion in the stools to return to normal, so that the delayed excretion was included in the balance figures.

Analytical Methods

The organization of a metabolism ward and the importance of rigid control of the patients and of the collection of the samples have been fully dealt with by Bassett, Eldon, and McCann (2) and need not be dealt with here.

The stools were collected for each three-day period in a covered jar, and at the end of the time 50 c.c. of concentrated nitric acid was added and stirred in. After standing for several days the contents of the jars were transferred to a large porcelain evaporating dish and slowly evaporated. When dry the dish with its contents was weighed in order to get a rough idea of the dry weight of the stool. The dish was then put on a sand bath and very slowly heated. As the contents dried a slow process of deflagration occurred, and finally a dry charred mass was left. The dish was cooled and weighed and the contents transferred to a mortar. The dish was then cleansed inside, dried, and weighed again. The difference between these last two weighings was called the 'deflagrated weight' and was the weight from which the sample of deflagrated stool was taken. The deflagrated stools were readily ground in the mortar to a very fine dust-like powder, which could be much more accurately sampled than is the case with any wet sampling method. The nitric acid overcame the difficulty of the fatty stool, which is sometimes a problem in other dry sampling methods. The only difficulty occurred if liquid paraffin was used, and this should not be administered. A sample of deflagrated stool was then weighed into a deep silica beaker and ashed in a muffle furnace for twelve hours at a temperature not exceeding 550° C. The beaker was cooled and weighed, this weighing being used to calculate the total mineral ash in the stool period. Concentrated hydrochloric acid was added to the beaker, which was gently heated for an hour covered by a watch-glass, in order to convert all the iron oxides into chlorides. Distilled water was added and the solution filtered

through ashless paper. The filter paper was put back into the beaker and ashed in the muffle furnace. The beaker was finally extracted several times with hot dilute hydrochloric acid and the whole filtrate made up to volume.

When large doses of iron are being given the method for determining iron must be capable of being used over a range which may vary from 10 mg. to 5 grm. in a three-day stool collection. It was found after long experience with the accepted Elvehjem (4) modification of the Kennedy method and other colorimetric methods that the number of factors influencing colour development and the subjective errors in colorimeter readings rendered all colorimetric methods inaccurate over such a range of iron. Klumpp's (8) modification of the titanium titration was found to be by far the most satisfactory method. By inserting both a macro and a micro burette into the system sketched by Klumpp, extreme accuracy could be maintained with any quantity of iron from 1 mg. upwards.

The calculation and tables presented were prepared on the assumption, confirmed by all workers on iron metabolism, that the urinary iron excretion is negligible. In view, however, of the unexpectedly high iron retention it was later considered advisable to analyse the urines which had been preserved against this eventuality by the addition of hydrochloric acid and chloroform. The urinary iron excretion was never found to exceed 1 mg. per day, which is a negligible amount compared with the figures for iron retention given in Table III, and it is therefore ignored.

Results

In Table III the iron retentions of the ten cases are summarized. The cases fall into two groups from the clinical aspect. In the upper group are the cases which were not anaemic and in which there was no reason to expect a state of iron deficiency. In the lower group are the cases which had an iron deficiency anaemia. In column 3 is given the number of days during which iron was administered, and in columns 4 and 5 the form of iron and the daily dose expressed in grains. The daily dose was always administered in three portions after meals. In column 6 is given in milligrams the actual intake of iron during the whole of the metabolism test after the commencement of iron therapy. A small fraction of this total is represented by the daily intake of iron in the food, which was constant throughout the whole test. The major fraction is represented by the therapeutic iron which was administered during only two or three of the metabolism periods. In column 7 the total iron retention is given. The method of calculating this as the difference between intake and output is shown in Tables I and II. In column 8 the iron retention is expressed in milligrams per day of iron therapy, and in column 9 as a percentage of the amount administered. In the anaemic cases the resultant increase in haemoglobin is shown in column 10. This was determined after a variable period during which no

further iron was administered. The iron content of the new haemoglobin is shown in column 11 calculated on a standard blood volume of 5 litres.

Discussion

The important point in the results is the large amount of iron which has been retained. The iron content of the whole circulating haemoglobin of an average adult is about 2.4 gm. Case 20 retained this amount in nine days. The non-anaemic cases also show high rates of retention, and Case 16 shows that the high rate of retention can be continued for considerable periods, leading to the accumulation of large amounts of iron in the body. Five weeks previously a six weeks' course of iron and ammonium citrate was concluded. Her percentage retention at that time should have been at least as great as in the later period. If it were the same, then she would have retained 7.93 gm. of metallic iron, which is $2\frac{1}{2}$ times the amount of iron in a circulating blood-volume of 5 litres.

• The amounts of iron retained are surprisingly high and necessitate a careful scrutiny of the technique. The actual intake of iron in each patient was checked in the following way. The iron was supplied to the ward either in solution or in capsules. In the former case the amount of solution supplied to the ward and the volume of the residue at the end of the experiment was measured in order to check the accuracy of the nursing staff. The dose of medicine was always measured by pipette. A similar check was kept on the capsules by supplying a bottle of capsules which were counted and weighed before and after the experiment. In each case a sample of the iron preparation was analysed.

In appendix 1 figures are given which show that there is no loss of iron in the preparation and analysis of the stool samples. Collection of the delayed excretion of iron as demonstrated in Tables I and II, ensures that the whole of the unabsorbed iron is collected.

Among published results of iron balance studies there is only one case in which really large doses of iron were used. Reznikoff, Toscanini, and Fullarton (11) put an apparently normal man on to iron and ammonium citrate in doses equivalent to 2 gm. of metallic iron daily and calculated the retention at 66.6 mg. daily, or 3.2 per cent. This is a little lower than Case 13 in the present series, who had a comparable iron intake. It is obvious, however, from Table III that there are wide differences between individuals.

Iron can accumulate rapidly in the body even when small doses are given. Reimann and Fritsch (10), using only 100 mg. of iron per day, found retentions of 1.46 gm. in twenty-eight days and 1.13 gm. in twenty-one days.

It is not surprising that iron should accumulate rapidly in the body when it is given in large doses by mouth, for, unlike the other minerals which enter the intestinal tract in large amounts, it is not excreted by the kidney

in appreciable quantity. Very little is known about the physiology of intestinal absorption, but the available evidence suggests that if there is a high concentration of an ionizable salt in the intestine it tends to be absorbed, and then either to be excreted in the urine or to accumulate in the tissues. Since iron is not appreciably excreted in the urine, it should accumulate in the tissues so long as a high concentration is preserved in the intestine. If the capacity to store iron is limited, it would be expected that re-excretion would occur via the bowel as soon as iron therapy was omitted. Unfortunately, the present experiments give no information as to whether this occurs or not.

It is known that the body can store large amounts of iron. In a case of pernicious anaemia Ashby (1) found 0.12 gm. per cent. in the liver, representing a total of 1.8 gm. of iron. Reznikoff, Toscanini, and Fullarton (11) studying a case of polycythaemia, found that, although phenylhydrazine caused a blood destruction equivalent to 2.1 gm. of iron, practically none of this was excreted. Ramage and Sheldon (9) found 50 gm. of iron in the body in a case of haemochromatosis.

It would obviously be fallacious to draw comparisons between cases in so small a series, but the results do suggest:

(a) That the size of the dose affects the amount retained. This is best seen by comparing cases 19 and 20, who had the same degree of anaemia.

(b) That there is a tendency to higher rates of retention in the anaemic cases. Every case with a retention greater than 10 per cent. is in the anaemic group.

(c) That if, as is claimed, ferrous preparations are better retained than the scale preparations, this is not a universal rule. Comparison of experiments A and B on case 16 suggests the reverse conclusion. Whipple and Robscheit-Robbins (14), were unable to find any difference in the retention of ferrous and scale preparations by dogs.

In the introduction it was stated that our only knowledge of the retention of large doses of iron given by mouth was indirectly derived from the resultant haemoglobin regeneration in certain cases of hypochromic anaemia. The ratio of the amount of iron contained in the newly formed haemoglobin to the amount of iron given by the mouth may be called the blood utilization of the iron. Heath, Strauss, and Castle (6) showed in a series of cases of hypochromic anaemia treated by injections of iron that the utilization of the injected iron was roughly 100 per cent. It has since been inferred by some as a corollary to the work of Heath, Strauss, and Castle, that the utilization of iron given by mouth in cases of hypochromic anaemia is a direct measure of the retention of the iron.

The results shown in Table III suggest that this inference is incorrect. The average utilization of iron in a series of cases can be calculated by comparing the average effective dose of iron with the average haemoglobin response. It will be generally agreed that when the haemoglobin of a case of hypochromic anaemia rises under treatment by 1 per cent. per day from

its initial level to 100 per cent. this response can be regarded as satisfactory and probably above the average. Such a haemoglobin rise represents the addition to the circulation of 23 mg. of iron per day. Using this figure the average utilization of iron has been calculated from published estimates of the average effective dose, and is given in Table IV. Heath (7) found in 84 cases, most of which were treated with 90 grains of iron and ammonium citrate daily, that the average percentage utilization over the entire period of recovery was 3.4 per cent. Fullerton (5) measured the haemoglobin rise of 33 patients during the first 25 to 40 days of treatment with 90 grains of iron and ammonium citrate. He found a percentage utilization of from 2.03 per cent. to 2.5 per cent. It may be taken, therefore, that the figures for utilization given in Table V are representative of general clinical experience. Comparison of Table IV with Table III shows a big discrepancy between utilization and retention.

The conclusion must therefore be drawn that with large doses of iron, utilization is not a measure of retention. Reimann and Fritsch (10), using small doses of iron given as ferrous chloride, found that in three cases out of five less than 45 per cent. of the retained iron was utilized.

It is obvious, therefore, that conclusions about the retention of iron drawn from the haemoglobin response in the hypochromic anaemias must be fallacious.

The figures given in Table III raise again the question why it is necessary to give iron in such large doses. It has been assumed that large doses are necessary in order to get enough iron into the body to allow the haemoglobin to be formed. Fullerton (5) considers that the work of Heath, Strauss, and Castle establishes this explanation, and he draws the further inference that the hypochromic anaemias are due solely to iron deficiency. The figures in Table III show that the first assumption is certainly incorrect, and throw doubt on the further inference.

It is important that the results reported here should not be regarded as evidence that large doses of iron are unnecessary. The value of large doses is already firmly established in clinical experience. What the results do mean is that the explanation previously given of the necessity for large doses is incorrect, and that the relationship between the hypochromic anaemias and a state of iron deficiency is not so simple as the work of Heath, Strauss, and Castle had led us to suppose.

Summary

1. The retention of orally administered iron has been studied by ten balance experiments in nine cases.
2. When large doses of iron and ammonium citrate or Bland's pill are used, large quantities of iron are retained.
3. The retention of iron is much greater than has been inferred from the rate of haemoglobin response.

4. The results of the experiments on the effect of large doses of iron on the metabolism of calcium and phosphorus will be communicated in another place.

During the conduct of these experiments one of us (J.F.B.) held the Leverhulme Research Scholarship of the Royal College of Physicians, and later, the Walter Dixon Research Scholarship of the British Medical Association.

We wish to express our appreciation to Professor F. R. Fraser for valuable criticism and advice, and to Miss Rose Simmonds of the metabolism ward of the London Hospital for her valuable assistance in the metabolism tests.

APPENDIX 1

The Deflagration Method

That there is no loss of minerals in the deflagration process was proved by taking, on a number of occasions, a stool after it had been treated with nitric acid, and stirring it with an electrically driven propeller for several hours until there was a homogeneous emulsion. Three or four small aliquots were taken into the silica beakers, and the remainder was dried down and put through the routine procedure. The silica beakers were evaporated dry and the contents ashed in the muffle furnace. The results obtained on the contents of the silica beakers were, therefore, a check on possible loss during the process of deflagrating the main bulk of the sample. The results obtained in this manner are given below.

Mineral Weight per Stool

Test number.	By deflagration process.	By wet aliquot.
1	Ca. grm. 2.91	2.95
	Fe. mg. 39.8	38.7
2	Ca. grm. 0.836	0.838
	Fe. mg. 12.27	12.43
3	Fe. mg. 1,279	1,262

Figures are given below to show that the titanium titration method gives results which are consistent, and compare very closely with the results obtained by gravimetric analysis.

1. 2.00 grm. of ferrous ammonium sulphate put through the process of ashing in muffle furnace and extraction with acid. Sample analysed by titanium trichloride method:

Iron content (theoretical)	. . .	285 mg.
Iron content (by analysis)	. . .	287 mg.
Error	. . .	+0.7 per cent.

2. Three stool collections from Case 11 were analysed for iron. At a later date it was suspected that the results were too high. The whole process was repeated, including ashing of the deflagrated stools, extraction of the ash with acid, and the titanium titration. The two sets of analyses agreed closely as below:

	1st analysis.	2nd analysis.	Difference.
Period I	2,474 mg.	2,470 mg.	-0.2 %
Period II	888 "	866 "	-2.5 "
Period III	1,647 "	1,630 "	-1.0 "
Total	5,009 "	4,966 "	-0.9 "

In order to test the possibility of the method giving consistently low results it was compared with the very tedious procedure of digesting the deflagrated stool with sulphuric acid and estimating its iron gravimetrically:

Three-day stool sample:

By wet ashing and gravimetric analysis	.	.	.	1,732 mg.
By dry ashing and titanium titration	.	.	.	1,713 mg.
Error	.	.	.	-1.1 per cent.

APPENDIX 2

Case Reports

Case 12. Female, aged 30. A case of unexplained choroiditis, otherwise in good health. Wassermann reaction negative. Blood count, r.b.c. 4,200,000, Hb. 78 per cent., C.I. 0.92, w.b.c. 8,600.

Case 13. Male, aged 21, single, cabinet-maker. A case of disseminated sclerosis in a fairly early stage. Throughout the whole of the experimental period he was having daily intramuscular injections of Boots' hepastab (liver preparation). Blood count, r.b.c. 5,130,000, Hb. 98 per cent., C.I. 0.96, w.b.c. 8,220.

Case 16. Female, aged 14½. Convalescent from rheumatic fever. Afebrile.

During the test *A* she was kept on the ward diet and her retention of Blaud's pill was measured. Immediately prior to this test she had been treated for six weeks on 90 grains daily of iron and ammonium citrate. The last residue of this was excreted in periods 1 and 2.

During the test *B* she was on a special diet and iron, phosphorus, and calcium were all estimated. The retention of iron and ammonium citrate was measured. At the start of test *A* her blood count was r.b.c. 5,000,000, Hb. 86 per cent., C.I. 0.86, w.b.c. 6,400.

Case 18. Male, aged 7. Convalescent from pleurisy. Afebrile.

Blood count, r.b.c. 5,000,000, Hb. 87 per cent., C.I. 0.87, w.b.c. 7,200.

Case 10. Female, aged 18, single. A case of hypochromic anaemia of unexplained origin. Diet moderately good. Catamenia not excessive. No other haemorrhage. Test meal: Free HCl 0.10, total acid 55 (without histamine): X-ray, no organic lesion of stomach or duodenum. Blood count on admission, r.b.c. 4,720,000, Hb. 42 per cent., C.I. 0.45, w.b.c. 7,700. After twelve days' treatment her haemoglobin was 76 per cent., and after a further three weeks without treatment it was 88 per cent. Subsequently she rose to 118 per cent. with further iron therapy, and has remained well for two years with occasional small doses of iron.

Case 17. Male, aged 18, messenger. A case of hypochromic anaemia associated with gastric ulcer. Had been treated two years previously for anaemia. Now complaining of lassitude and epigastric discomfort. Test

meal: Free HCl 0.26, total acid 85: X-ray, large lesser curve ulcer. Occult blood test negative on numerous occasions throughout his stay in hospital. Blood count on admission, r.b.c. 5,370,000, Hb. 62 per cent., C.I. 0.6, w.b.c. 7,200. After ten days' iron therapy his haemoglobin was 86 per cent., and after another three weeks without iron 92 per cent. It subsequently rose to 100 per cent., and the patient writes two years later to say he is still in good health. The explanation of the iron equivalent of his haemoglobin rise being greater than the iron retained is probably that, the patient being very small, his blood volume was less than the standard figure of 5 litres used in the calculation.

Case 19. Female, aged 55, widow. A case of idiopathic hypochromic anaemia. Complaint: weakness and shortness of breath.

Always pale since girlhood. Diet moderately satisfactory. Menopause six years previously. No recent blood loss. Finger nails brittle. Test meal: Free HCl 0.15 per cent. (without histamine): X-ray; no abnormality of stomach or duodenum. Blood count on admission, r.b.c. 5,820,000, Hb. 48 per cent., C.I. 0.41, w.b.c. 7,330. After nine days' treatment with iron her haemoglobin was 74 per cent. Iron therapy was continued for four months, and she has remained at about 100 per cent. haemoglobin for two years.

Case 20. Female, aged 30, single. A case of idiopathic hypochromic anaemia.

Slow onset of pallor and shortness of breath. Diet moderately satisfactory. Catamenia not excessive. Test meal: after gruel no free HCl, after histamine free HCl 0.25, total acid 82: X-ray; no abnormality of stomach or duodenum. Blood count on admission, r.b.c. 3,460,000, Hb. 45 per cent., C.I. 0.86, w.b.c. 3,800. She had iron for nine days, and four days later her haemoglobin was 74 per cent. It later rose to 100 per cent. with further iron therapy.

Case 21. Female, aged 38, single. A case of idiopathic hypochromic anaemia.

Two years' lassitude, pallor, and shortness of breath. Koilonychia. Diet moderately good. Catamenia not excessive. Test meal: Free HCl 0.15 (after histamine) total acid 30: X-ray; no abnormality of stomach or duodenum. Blood count on admission, r.b.c. 4,900,000, Hb. 55 per cent., C.I. 0.56, w.b.c. 5,500. She was given iron for nine days, and after another week the haemoglobin was 68 per cent. Further rise was slow, and she did not reach 100 per cent. until she had had five months' continuous treatment. She has remained well for two years with occasional iron therapy.

TABLE I

Case 13 (W. Y.) Calcium, Phosphorus, and Iron Balance. Three-day Periods. Reduced Iron administered during Periods 4, 5, and 6. All Figures expressed in gm. per Period except Iron Figures in mg. per Period. U = Urine, F = Faeces, T = Total.

Stage No.	No.	Metabolism period.			Intake.			Excretion.			[14]		
		Date.	Therapy.	Fe.	Ca.	P.	Food.	Therapy.	Total.	Dry wt.	Mineral ash.		
1	1	Apr. 11-13	Nil	—	6.99	7.32	36	—	36	67	14.79	0.78	2.58
	2	" 14-16	Nil	—	"	"	"	—	36	107	14.98	0.77	3.33
	3	" 17-19	Nil	—	"	"	"	—	36	128	16.73	1.00	3.37
2	4	" 20-22	Reduced iron	4,800	"	"	"	4,800	4,836	127	24.14	1.04	3.28
	5	" 23-25	"	7,200	"	"	"	7,200	7,236	143	28.04	1.02	3.05
	6	" 26-28	"	9,536	"	"	"	9,536	9,572	130	32.48	1.02	3.59
3	7	" 29 to May 1	Nil	—	"	"	"	—	36	91	15.10	0.87	3.05
	8	" 2-4	Nil	—	"	"	"	—	36	75	13.95	0.96	2.68
	9	" 5-7	Nil	—	"	"	"	—	36	98	13.03	—	—

Iron Retention as a Result of Therapy.

Iron intake periods 4-7 mg.	21,680
Iron output periods 4-7 mg.	20,785
Total mg.	895
Retention as a result of 9 days' therapy } Per day mg.	99
% of intake	4

TABLE II

Case 16 a. *Iron Balance for 24 Days. Bland's Pill 30 gr. Three Times a Day administered for 9 Days. Figures expressed in mg.*

Stage. No.	Metabolism period.			Iron intake.			Iron output.
	No.	No. of days.	Therapy.	Food.*	Therapy.	Total.	Stools.
1	3	3	Nil	24	—	24	35
	4	3	Nil	24	—	24	43
	5	3	Bland's pill 30 gr. bds.	24	1,548	1,572	1,033
2	6	3	" "	24	1,548	1,572	1,800
	7	3	" "	24	1,548	1,572	1,341
	8	3	Nil	24	—	24	135
3	9	3	Nil	24	—	24	23
	10	3	Nil	24	—	24	18

Summary.

Iron balance	}	Intake	4,740
Periods 5-8		Output	4,309
Iron retention		Total	431
resulting from 9	}	Per day	48
days' therapy		% of intake	9

* approximate.

TABLE III

Retention of Iron given by Mouth

Case. No.	Age.	Iron therapy.		Daily dose gr.	Total iron content mg.	Iron retention.			Haemoglobin rise.	
		Number of days.	Form of iron.			Total mg.	Per day mg.	% of intake.	% Haldane.	Iron equiva- lent.
1	2	3	4	5	6	7	8	9	10	11
12	38	6	Bland	90	3,228	343	57	11	—	—
13	21	9	Reduced iron	45	21,680	895	99	4	—	—
16 a	14	9	Bland	90	4,740	431	48	9	—	—
16 b	14	6	Iron ammonium citrate	120	10,807	1,034	172	10	—	—
18	7	10	Iron ammonium citrate	80	12,216	911	91	8	—	—
10	18	12	Bland	90	6,000	1,118	93	18	42-88	1,058
17	16	10	Bland	90	5,500	639	64	11	62-92	690
19	55	9	Bland	50	3,366	1,069	119	32	48-74	598
20	30	9	Bland	125	8,325	2,491	277	30	45-74	667
21	38	9	Iron ammonium citrate	90	11,280	1,665	185	15	55-68	299

TABLE IV

Average Utilization of Large Doses of Iron in the Hypochromic Anaemias calculated from Published Accounts of the Average Effective Dose.

Preparation.	Authority.	Average effective dose.	Iron content.	Utilization.
Iron and ammonium citrate	Heath	90 gr.	1 grm.	2.3 %
Iron and ammonium citrate	Dameshek			
Reduced iron	Witts	60 gr.	0.8 grm.	2.9 %
Reduced iron	Dameshek	?	3.0 grm.	0.77 %
Blaud's pill	Schulten	90 gr.	4.8 grm.	0.48 %
	Witts	45 gr.	0.3 grm.	7.7 %

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ACROMEGALY AND CREATINE-CREATININE METABOLISM¹

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It has been shown by animal experimentation that there is a defect in the creatine-creatinine economy following alterations in the functions of the anterior lobe of the pituitary gland. Braier (1) demonstrated a decrease in the excretion of urinary creatinine in hypophysectomized dogs, while Schrire and Zwarenstein (2 and 3) produced increased elimination of creatinine in the urine of rabbits subsequent to injections of extracts of the anterior lobe of the pituitary. They could show no change in the excretion of creatine.

Collip (4) injected rats with thyreotropic hormone, and found an increase in the excretion of creatine in the urine, but observed no change in creatinine elimination. In a single case of acromegaly Schrire and Zwarenstein (5) found large quantities of both creatine and creatinine in the urine. It was therefore decided to investigate the creatine-creatinine metabolism of subjects suffering from recognized disorders of pituitary function. The purpose of this paper is to describe the results obtained in such subjects, together with control investigations, and to discuss the results in the light of previous animal experiments.

Methods and Material

Quantitative estimations of creatine and creatinine in the urine were determined by Folin's colorimetric method. Urine was carefully collected over periods of twenty-four hours from 8.0 a.m. one day to 8.0 a.m. the following day; samples of the collection were utilized for determination of creatine and creatinine. The values of the daily excretions are noted in terms of grammes per twenty-four hours. Particular care was exercised in the collection and measurement of the urine, the subjects passing urine before going to stool.

The subjects were placed upon a creatine-free diet which was prepared by Miss Verdon-Roe, dietician to the Unit. I wish to express thanks to her for help in this study. On occasions an ordinary diet was substituted; such a change has been noted in the text.

¹ Received September 15, 1936.

The investigations were conducted on nine cases of acromegaly. All the subjects were ambulant and quite active. Two subjects, each with a chromophobe adenoma of the pituitary, were used as controls, together with four subjects exhibiting raised intracranial pressure. Eight normal subjects were used for injection of different extracts of the anterior lobe of the

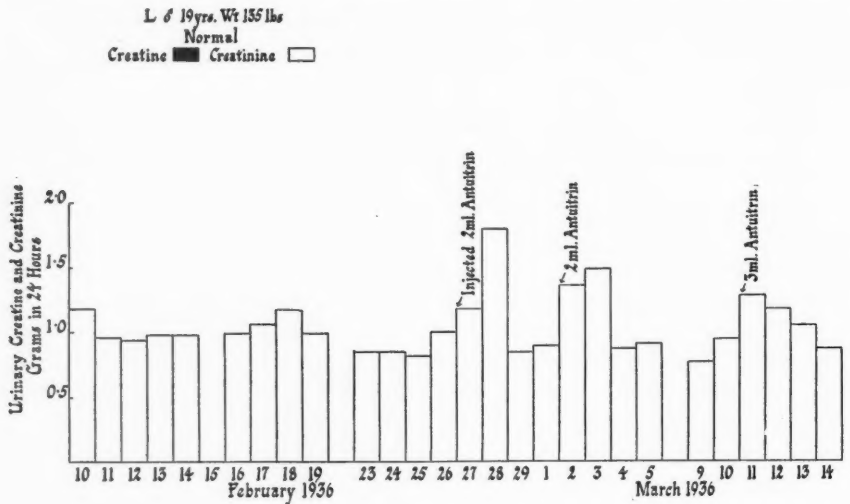


FIG. 1.

pituitary. Each had a normal metabolism of creatine and creatinine. These normal cases were also ambulant. Two extracts of the pituitary were utilized for injection, both prepared from the anterior lobe. One extract (Schering-Kalbaum, and Organon) contained thyreotropic hormone, and the other 'antuitrin' (Park Davis) had no demonstrable thyreotropic activity.

Results

A. *Injection of antuitrin in normal subjects.* It was considered necessary to repeat injections of the pituitary principles in normal human material to determine whether the effects would conform with those obtained in animal experiments.

Fig. 1 shows the results obtained in a normal adult male with injections of antuitrin. The subject was injected intramuscularly on the 27th February, on the 2nd March with 2 ml. antuitrin, and on the 11th March with 3 ml. antuitrin. The period previous to the injection shows an output of creatinine which is normal in quantity and regularity. When each injection was made the creatinine excretion rose significantly and returned to normal in a day or two. No creatine was detectable in the urine before, during, or after the injections.

In all, fifteen injections of antuitrin were made on eight different subjects. Of these twelve produced a well-marked increase of excretion of creatinine; three produced a less-marked rise of creatinine excretion. After injection of antuitrin a phase of polyuria was present in all these subjects.

B. *Injection of thyreotropic hormone in normal subjects.* This material was

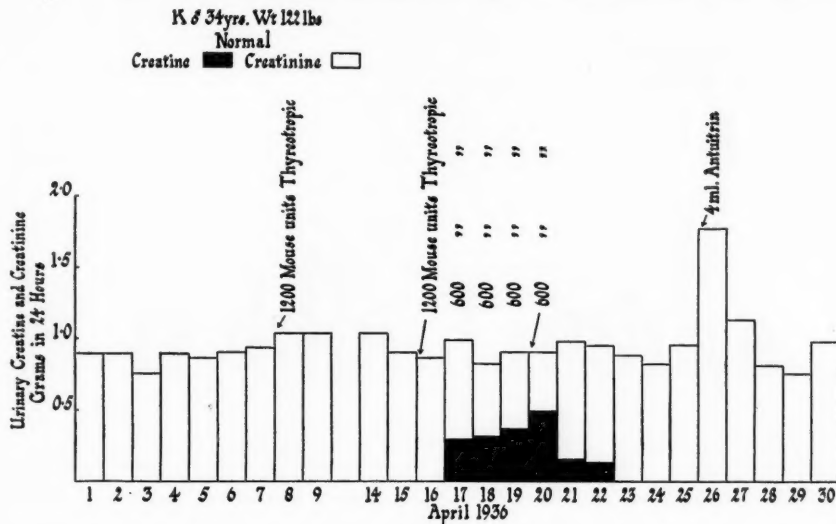


FIG. 2.

tried on four subjects. Fig. 2 presents the effect on creatine excretion in one of these individuals which is typical of the results obtained in all.

The subject was a normal adult male. The creatinine excretion from the 1st to the 16th April was normal in output and regularity. On the 8th he was given a trial dose of thyreotropic hormone intramuscularly, with no effects. On the 16th, and on the four following days, he was injected with thyreotropic hormone. The creatinine excretion was unchanged, but creatine appeared in the urine in large quantities. Before and after each series of injections no creatinuria was detectable, except in the two days immediately following the injection period. During the injection phase creatine appeared in the urine to the extent of 0.4 gm. in twenty-four hours.

On the 26th the subject received an injection of antuitrin (4 ml.), which produced a large increase in creatinine excretion but had no effect on the creatine in the urine.

In one of the cases investigated creatine was eliminated in the urine (after a course of injections) to the extent of 0.646 gm. in twenty-four hours, and continued to be present in the urine for four days after the last injection.

C. *Creatine ingestion.* Creatine in 5 gm. doses was administered to normal subjects on six occasions. The amount returned in the urine varied from 16 to 24 per cent. of the dose, an average of 19 per cent.

Case 2 was investigated over a period of twenty-eight days; the results

are charted in Fig. 4. She was 180 lb. in weight, and was diagnosed clinically as suffering from acromegaly. The results obtained are similar to those of Case 1.

The results indicate that, on fourteen out of twenty-five occasions when the urine was collected and examined, creatinine excretion exceeded 1.5 gm. in twenty-four hours. On five occasions it was over 1.9 gm., and on two occa-

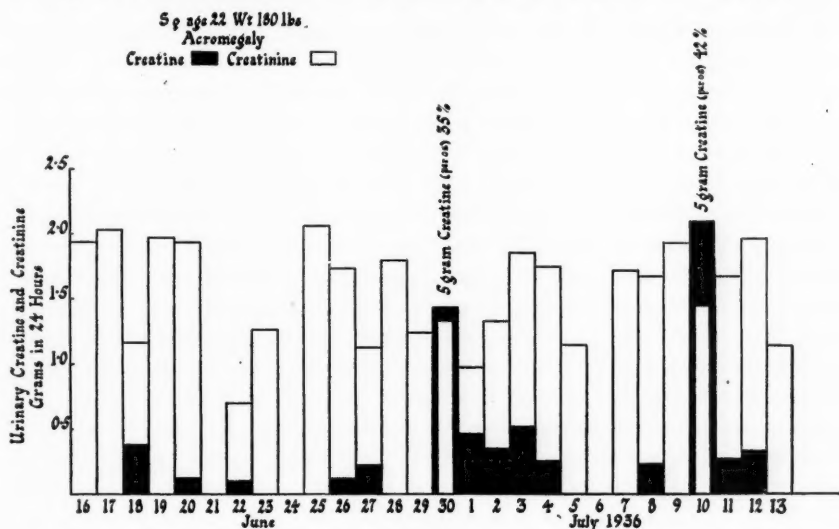


FIG. 4.

sions the 2.0 gm. level was passed. These quantities are much beyond the output for normal females. A normal woman of similar weight to this subject should eliminate less than 1.4 gm. creatinine in the urine daily. The fluctuations in the excretion of creatinine were marked. The lowest level reached was 0.7 gm. in twenty-four hours, and the highest level attained was just under 2.1 gm. There was thus a variation of 1.4 gm. between the two levels of excretion.

Creatine excretion was not as marked as in Case 1, but, on occasions, a level of excretion as high as 0.5 gm. in twenty-four hours was reached. The elimination of creatine was inconstant in this subject, no creatine being detectable in the urine on many days; its excretion was very irregular too, and of a degree not usually found in normal individuals.

On two occasions creatine was administered per os in 5 gm. doses. The first time 35 per cent. of the dose was excreted as such, and the second time 42 per cent. was returned in the urine. This subject never passed sugar in the urine throughout the period of investigation.

The seven other cases of acromegaly all showed similar results. Three were subjects exhibiting all the signs of acromegaly, and during the period of the investigation received no therapy. Two others were operated on, and observations on the creatine and creatinine excretion were obtained in the

pre- and post-operative state. Two subjects were investigated in a post-operative state only. Six of these seven cases showed clear-cut results which conformed with those obtained in the two detailed cases. The creatinine excretion was inconstant and grossly excessive relative to the body-weight. The creatine elimination was most irregular and usually present in abnormally large quantities. On twelve different occasions 5 gm. doses of creatine were given to the nine cases of acromegaly. On the average 38 per cent. of the dose appeared as such in the urine, and the amounts varied from 27 to 55 per cent.

One subject exhibited the fluctuations in output of creatine and creatinine as well as the decreased tolerance to ingested creatine, but the creatinine level was only on a few occasions higher than the normal. Of the two subjects operated on, one showed a return of creatinine excretion to normal, and the level of excretion was reduced to that found in a normal person of similar body-weight, and the excretion of both creatinine and creatine became constant and regular. The second case operated on exhibited no change in excretion in the post-operative stage.

In only one of these seven subjects was it possible to demonstrate a hyperglycaemia and a glycosuria. In this case the output of glucose in the urine was as great as in that described in detail.

In all cases the volume of urine was increased.

Controls

Control investigations were performed on two types of cases:

- (a) Subjects with raised intracranial pressure.
- (b) Subjects with intrasellar tumours, not eosinophilic in type.

The four subjects with raised intracranial pressure had severe headaches, occasional vomiting, papilloedema, and signs referable to a neoplasm located in one or other hemisphere. All had a normal creatinine output. The creatinine excretion in the urine was within normal limits, was constant, and exhibited none of the fluctuations seen in subjects with acromegaly. Creatinuria was present periodically, but never excessively.

Only two subjects of the second type were available. Both were cases of chromophobe adenoma of the pituitary. In each, the quantity of creatinine excreted was within normal limits. There was, however, a gross fluctuation in output comparable to that evidenced in acromegaly. Creatine was present in the urine of one subject in moderate amounts on several occasions.

Discussion

Increased excretion of creatinine in the urine of gonadectomized rabbits was demonstrated by Schrire and Zwarenstein (3 and 7). This effect was not immediate in onset, but became apparent after a period of two to four

months in males, and seven to nine months in females. That the mechanism of production of this post-castration rise of creatinine in the urine was hormonal in character was shown by injecting gonadal extracts into male and female castrates, and by grafting testes into castrated males (Schrire and Zwarenstein (3, 7, and 8). In such experiments the creatinine excretion returned to normal, which was taken to indicate a successful replacement of gonadal secretion.

Following castration, hypertrophy of the anterior lobe of the pituitary becomes apparent after a lapse of two to four months in a male, and seven to nine months in a female, rabbit. This time period is concomitant with the latent period observed before there is a post-castration increase in creatinine excretion. As the works of Schrire and Zwarenstein (2 and 3) had shown that, in animals, the secretions of the anterior lobe affected the creatinine excretion by increasing it, it was suggested that gonadectomy acted by removing an inhibitory control exerted by the gonads upon the secretion of the pituitary gland. It is possible, therefore, that the hypertrophy of the pituitary gland in gonadectomized animals accounts for the increased elimination of creatinine in the urine. It was further shown by Schrire and Zwarenstein (2) that parenteral administration of creatine to castrated rabbits resulted in an excessive return of creatine in the urine of such animals as compared with the normal animals. Remen (9), Lasch (10), Buhler (11), and Schittenhelm and Buhler (12) have also shown that there is a diminished tolerance to creatine in functionally castrated human subjects. The cause of this alteration was presumed to depend upon the alteration in the secretion of the pituitary gland following castration. This work suggested that a study of the creatine-creatinine economy in the human would be of especial interest when the pituitary gland was known to be abnormally functioning, or in the presence of injected extracts of the pituitary gland. The results of the injection of anterior lobe extracts into normal subjects recorded here are similar to those obtained in animals by Collip and by Schrire and Zwarenstein. Antuitrin, on twelve out of fifteen occasions, promoted a significant increase in creatinine excretion in the urine, but on three occasions the results were not well marked. This may be explained by the lack of standardization of the extract, there being no satisfactory method for assuring that the extract contained in each ampoule has the same potency. Thyreotropic hormone, when injected into human subjects, produced a marked creatinuria but had no influence on creatinine excretion. A similar effect can be produced with thyroid extract and thyroxin. It is also noteworthy that, in exophthalmic goitre there is an increase in creatine and not in creatinine excretion. These observations indicate that there are at least two factors in the pituitary gland which control the metabolism of creatine and creatinine. One factor (thyreotropic) is effective via the thyroid and promotes creatinuria but no increase in creatinine excretion, and the other factor produces increased elimination of creatinine but not of creatine in the urine.

In the study of the results obtained from the subjects with acromegaly four features are conspicuous:

1. Creatinine excretion is excessive in amount.
2. Creatine excretion is excessive in amount.
3. The output of creatinine and creatine is extremely irregular.
4. There is a diminished tolerance to creatine by mouth.

In eight out of nine cases (and less marked in the ninth case) creatinine was present in the urine in quantities which were in excess of the normal. The excretion of this substance is dependent on, and proportional to, the body musculature; and when the excretion of the subjects examined is related to their weight, there is no doubt as to the gross abnormality of excretion of creatinine. The experiments performed on animals by Schrire and Zwarenstein, and the results obtained with injection of pituitary principles in this investigation, have shown how the anterior lobe is responsible for increased amounts of creatinine in the urine. It may therefore be deduced that the hypertrophied eosinophilic elements of the pituitary in acromegaly may be secreting additional quantities of that factor which is producing the increment in urinary creatinine. In the normal male adult creatine is seldom present in significant quantities in the urine. In the female there is a continuance into adult life of the creatinuria which is present in both sexes before puberty. This is present in minor quantities, is irregular in appearance, and should not exceed 200 mg. in twenty-four hours.

In the urine of an acromegalic subject, either male or female, there is a marked creatinuria which is well above the normal levels. Case 1 and the records of the other subjects in the appendix show this feature very well indeed. Previous results have shown how thyrotropic hormone and thyroid extracts produce a creatinuria unassociated with an elevation of the creatinine in the urine. The findings obtained suggest that the large amounts of creatine in the urine may be due to hypersecretion of thyrotropic substances from the eosinophilic elements in the pituitary tumour.

This study of subjects with acromegaly therefore suggests that there are two factors in the pituitary; one elevates the creatine in the urine, possibly via the thyroid, and the other controls creatinine; but both are independent in their action.

In a normal individual it is generally accepted that about 20 per cent. of a 5 gm. dose of creatine is returned as such in the urine (Cameron (13)), though some investigators have obtained higher values. In the cases examined during this investigation the values obtained conformed with those of Cameron. The average output in the normal subjects of this investigation was 19 per cent. of the ingested dose. In the subjects with acromegaly 38 per cent. of the dose was excreted as creatine in the urine, this being the average figure obtained from twelve results, with a variation from 27 to 55 per cent. These results were similar to those obtained in castrated rabbits and suggested that the intolerance to creatine ad-

ministered per os, exhibited by the acromegalic subjects, was dependent on the increased secretion from the tumour eliminating creatine from the organism. Any factor which produces hyperfunction of the anterior lobe of the pituitary, whether it is primary in the pituitary or secondary to gonadal failure, will be indicated by an intolerance to ingested creatine.

In healthy individuals on a creatine-free diet the output of creatinine is a constant quantity for each, and is independent of quantitative changes in the total amount of nitrogen eliminated. The variations in output are small and any marked deviation is abnormal. In acromegaly a striking feature is the gross fluctuation in creatinine excretion. Similarly in acromegaly there is a marked irregularity in excretion of creatine which is above that of the normal.

The reason for this inconstant output of both creatinine and creatine is not known, but the observations recorded in this series suggest two possible explanations. Firstly, it is possible that the hormonal output of the eosinophilic adenoma may not be steady and constant. Secondly, it may result from the direct effects of increased intrasellar pressure playing an important role in determining the quantities of secretion liberated by the remaining elements of the pituitary gland. In the two cases with a chromophobe adenoma, the fluctuation in creatinine excretion was comparable to that observed in the subjects with acromegaly, although the quantities were within the normal limits of excretion. No evidence was obtained that increased intracranial pressure alone caused this fluctuation. If the first suggestion is the correct one, then the quantitative differences in creatine and creatinine output observed in the subjects suffering from acromegaly may be related to the stage of the disease. More advanced cases, in which there would be a greater amount of eosinophilic elements, showed greater irregularity in, and increased quantities of, creatinine excretion.

Again, of the two cases operated on, one showed a striking return of the creatine-creatinine metabolism to normal, the post-operative excretion levels being similar to those found in a healthy individual. The other subject exhibited little or no change; but this was to be expected, as before operation there was not an excessive creatinine output. It is therefore probable that the state of the tumour, from its secretory aspect, determines the degree of abnormality of the creatine-creatinine metabolism.

The different results in cases of acromegaly and in those with chromophobe adenoma suggest a method of aid in deciding the nature of a pituitary tumour. The increased creatinine excretion, the increased creatinuria, the diminished tolerance to creatine, and the gross irregularity in output of both substances seem to be characteristic of acromegaly. More important, the grade of disturbance may be helpful in estimating the activity and growth of the tumour, and prove a decisive factor in advising against or for operative interference in the absence of signs involving the visual pathways.

The source of the increment in creatine and creatinine excretion in the

urine in acromegaly and subsequent to injection of the pituitary hormones is not quite clear. However, as the subjects were maintained on a creatine-free diet, creatine and creatinine must be derived from changes in the muscles or possibly from alterations in kidney function.

Summary

1. The creatine-creatinine metabolism of nine cases of acromegaly has been studied.
2. Creatinine and creatine appear in abnormally high quantities in the urine.
3. The output of creatinine and creatine is irregular and inconstant.
4. There is an intolerance to creatine administered per os.
5. The effect of pituitary extracts on creatine and creatinine metabolism has been studied in normals.
6. These results have been discussed. It is suggested that there are two hormones in the pituitary gland, each playing a part in creatine and creatinine metabolism.

It is a pleasure to thank the Medical Research Council and the physicians of the National Hospital, Queen Square, for granting me facilities to carry out this work. To Dr. E. Arnold Carmichael I extend my thanks for his friendly advice and help during this investigation; and to Messrs. Schering, Kahlbaum and to Dr. Alison Macbeth of Messrs. Organon for supplies of thyreotropic hormone. I also wish to acknowledge my indebtedness to Dr. L. Mirvish of Capetown.

These investigations were performed during the tenure of the H. B. Webb Research Scholarship from the University of Capetown, South Africa.

APPENDIX

Subjects with Acromegaly

Case 1. J. E., male. Aged 45. Weight 185 lb. Came under the care of Dr. Louis Mirvish (of Capetown), complaining of polyphagia, polydipsia, and polyuria. The symptoms were of several months' duration. The face was coarse, the nose big; there was marked prognathism, with separation of the teeth in the lower jaw. The feet were progressively enlarging, requiring increasing sizes in shoes. The optic disks were normal. X-ray of the skull showed an enlarged pituitary fossa with erosion of the clinoid processes.

Fig. 3 is the chart of the results.

Case 2. D. S., female. Aged 22. Weight 180 lb. Was admitted on the 11th June 1936 to the National Hospital under the care of Dr. Kinnier Wilson, complaining of excessive growth of the whole body of seven years' duration and of severe headache of three years' duration. At the age of 15 her feet began to grow larger, and now necessitate size 11 in shoes. Her hands also grew larger. She rapidly increased in height. Her appetite and thirst were unusually great and urinary frequency was increased. Menstruation

had been regular till one year previous to admission. Her features were large and coarse, with thick lips; the hands and feet were large. The lower jaw had become enlarged and more prominent. The fields of vision and optic disks were normal. X-ray of the skull showed no enlargement of pituitary fossa.

Fig. 4 is the chart of the results.

Case 3. G. T., female. Aged 57. Weight 130 lb. Was admitted on the 22nd April 1936 to the National Hospital, under the care of Dr. E. Arnold Carmichael, for observation. Her illness commenced several years previously, when she observed a progressive increase in the size of her hands and feet, associated with headache. On examination her features were coarse, with a protruding lower jaw in which the teeth were widely spread. Her hands and feet were large. The fields of vision and optic disks were unaffected. X-ray of the skull demonstrated an enlarged sella turcica.

The results of the investigations were as follows:

Date.	Creatinine gram./24 hr.	Creatine gram./24 hr.	Sugar gram./24 hr.
23.4.36	0.78	0.39	—
24.4.36	1.4	0.183	78
25.4.36	0.788	0.262	—
26.4.36	1.8	0.54	—
27.4.36	Lost	—	—
28.4.36	0.90	0.139	—
29.4.36	0.878	0.526	161
30.4.36	0.65	0.4	130
1.5.36	1.026	0.256	119
2.5.36	2.0	0.17	96
3.5.36	1.31	0.455	73
4.5.36	0.975	1.955	133
5.5.36	0.60	0.171	108
6.5.36	1.235	0.221	168
7.5.36	0.747	0.498	188
8.5.36	0.90	0.15	—
9.5.36	0.922	1.508	—
10.5.36	0.819	0.399	—
11.5.36	1.8	0.552	—
12.5.36	0.855	0.285	154
13.5.36	0.678	1.35	—
14.5.36	1.12	0.95	—
15.5.36	0.72	0.121	84
16.5.36	0.946	0.616	—
17.5.36	1.47	0.151	—
18.5.36	0.836	0.626	—
4.5.36—5 gram. creatine per os (39 % eliminated)			
9.5.36—5 " " " (34 % ")			
13.5.36—5 " " " (40 % ")			

Case 4. L. N., female. Aged 29. Weight 165 lb. Was admitted in February 1936 to the National Hospital, under Dr. E. Arnold Carmichael. In 1927 she began to be troubled with headaches and loss of vision. At that time she had definite increase in size of hands and feet, along with prognathism. The fields showed a bitemporal constriction. In 1927 Radon

seeds were implanted in the pituitary gland. In 1929 deep X-ray therapy was used, and six months later, at operation, part of the pituitary gland was removed. She returned on the 10th February 1936 complaining of headaches. The skin of the face was thick and coarse, with marked hirsutism, necessitating shaving every few days. Prognathism was marked, and the teeth of the lower jaw were widely separated. The hands were thick and spade-shaped, and the feet were large. Her menstrual periods were regular, but the flow was scanty. Sugar was never found in her urine, and the blood curve was normal. X-rays showed eroded clinoid processes with an enlarged pituitary fossa.

The results of the investigation are tabulated below :

Date.	Creatinine gm./24 hr.	Creatine gm./24 hr.
11.2.36	1.8	0.144
12.2.36	1.11	0.277
13.2.36	1.16	0.37
14.2.36	2.2	—
15.2.36	1.12	0.145
16.2.36	1.24	0.339
17.2.36	1.819	0.317
18.2.36	1.305	0.201
19.2.36	1.125	0.113
20.2.36	1.26	0.54
21.2.36	1.66	2.765
22.2.36	1.42	0.56
23.2.36	1.38	0.12
24.2.36	1.305	nil
25.2.36	1.295	1.543
26.2.36	1.38	0.125
27.2.36	2.0	0.121
21.2.36—5	gram. creatine per os (55 % eliminated)	
25.2.36—5	,, ,, ,, (34 % ,,)	

Case 5. H. V., female. Aged 28. Weight 145 lb. Was admitted in May 1936 to the National Hospital, under the care of Dr. Gordon Holmes, complaining of headaches. She had marked prognathism, with well-separated teeth in her lower jaw. Her hands and feet were large and bulbous, particularly her big toes. There was a marked amount of hair on the forearms and legs and a slight amount on her upper lip. The skin was coarse and inelastic. The optic disks were normal and her fields of vision full. There was complete amenorrhoea. X-ray of the skull showed an enlarged sella turcica. At operation by Mr. Julian Taylor a part of the pituitary tumour was excised.

Her results before and after operation are tabulated below. There is a remarkable change to normality after the operation in the creatinine output and regularity.

Date.	Creatinine gm./24 hr.	Creatine gm./24 hr.
31.5.36	1.26	0.329
1.6.36	1.20	0.51
2.6.36	1.9	0.616
3.6.36	0.562	0.11
4.6.36	0.93	0.21

Date.	Creatinine gm./24 hr.	Creatine gm./24 hr.
5.6.36	1.708	0
6.6.36	0.81	0
7.6.36	1.21	0.551
8.6.36	1.90	0.288
9.6.36	0.90	0
10.6.36	1.23	1.45
12.6.36—Operated		
16.6.36	0.648	0.162
17.6.36	0.611	0.211
18.6.36	0.834	0.498
19.6.36	0.832	0
20.6.36	0.612	0
21.6.36	0.684	0.171
22.6.36	0.45	0
23.6.36	0.744	0
24.6.36	0.759	0
25.6.36	1.008	0
26.6.36	0.687	0
27.6.36	0.798	0.31
28.6.36	0.51	0.24
29.6.36	0.93	0.176
30.6.36	0.75	0.15
1.7.36	0.87	0
2.7.36	0.75	0.15
3.7.36	0.75	0.092
4.7.36	0.915	0
5.7.36	0.669	0.111
10.6.36—5 gm. creatine per os (29 % + eliminated)		

Case 6. P. F., female. Aged 23. Weight 170 lb. Was admitted to the National Hospital, under the care of Dr. Gordon Holmes, complaining of increased growth of the feet of two and a half years' duration and pains in the head of three to four years' duration. Her nose was big and prominent and prognathism was marked. Both upper and lower teeth were unduly spaced. Her hands and feet were broad and spade-like. Both optic disks were pale, the left extremely so. Examination of the fields of vision showed that there was bilateral temporal hemianopia. Menstruation became irregular three to four years ago, and for two and a half years there had been complete amenorrhoea. X-ray of the skull showed a wide area of bony absorption in the region of the posterior clinoid.

The results are tabulated below :

Date.	Creatinine gm./24 hr.	Creatine gm./24 hr.
24.6.36	1.62	0.34
25.6.36	2.1	0
26.6.36	1.08	0.31
27.6.36	1.14	0.47
28.6.36	1.80	0.244
29.6.36	1.248	0
30.6.36	1.125	1.875

Date.	Creatinine gram./24 hr.	Creatine gram./24 hr.
1.7.36	0.90	0.60
2.7.36	1.65	0
3.7.36	1.43	0
4.7.36	1.26	0
5.7.36	—	—

30.6.36—5 gram. creatine per os (37 % eliminated)

Case 7. L. S., female. Aged 22. Weight 120 lb. Was admitted to the New Somerset Hospital, Capetown, under the care of Professor Falconer. She complained of headache and absent menstrual periods of three years' duration. She had large coarse hands, big feet, and prominent heels. There was moderate prognathism and slight spacing of teeth. The fields of vision evidenced bitemporal hemianopia; the edges of the optic disks were blurred. X-ray of the skull showed erosion of the posterior clinoid processes with enlargement of the pituitary fossa itself.

Only four estimations of urinary creatine and creatinine were made and are as follows:

Date.	Creatinine gram./24 hr.	Creatine gram./24 hr.
6.6.34	1.664	0.713
12.6.34	1.50	0.20
19.6.34	1.182	0.532
5.7.35	1.74	1.044

Case 8. B. H., female. Aged 47. Weight 112 lb. Was examined through the courtesy of Dr. S. Nevin of Maida Vale Hospital. She was a typical case of acromegaly, of several years' duration, with prognathism, large hands and feet, kyphosis, and scoliosis. She had bilateral anosmia. She was blind in the left eye and had full vision in the right eye. The left eye showed optic atrophy. X-ray of the skull revealed erosion of the clinoid processes and a large sella turcica. In September 1933 she received deep X-ray therapy to the sella. In August 1934 she was operated on, when part of the pituitary gland was removed. In July 1935 the acromegalic condition had been checked clinically.

The results are tabulated below:

Date.	Creatinine gram./24 hr.	Creatine gram./24 hr.
6.7.36	1.47	0
7.7.36	1.065	0.11
8.7.36	0.921	0.31
9.7.36	1.551	0
10.7.36	1.065	0
11.7.36	0.81	0
12.7.36	0.60	0.11
13.7.36	0.801	0.45
14.7.36	0.885	0
15.7.36	1.41	0.29

Sugar—on all occasions nil.

Case 9. G. K., male. Aged 33. Weight 135 lb. Was admitted, in March 1936, to the National Hospital, under the care of Dr. Purdon Martin, complaining of pain at the back of the eyes and ears, of growth in size of

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hands, all of three years' duration. The ears, nose, and jaw were enlarged and the hands and feet were bigger than normal. There was limitation in the temporal field of vision of the left eye. The left optic disk was pale. X-ray of the skull showed some erosion of the clinoids and over the pituitary fossa. Mr. Jefferson operated on the 22nd April 1936 and evacuated a soft pituitary adenoma. Dr. Greenfield reported that the tissue was an adenoma, consisting mainly of eosinophilic cells.

Below are tabulated the results of the investigation before and after operation:

Date.	Creatinine gram./24 hr.	Creatine gram./24 hr.
8.3.36	1.575	0
9.3.36	1.357	0.025
10.3.36	0.989	0
11.3.36	1.05	0.131
12.3.36	1.11	0
13.3.36	1.2	0
14.3.36	1.26	0
15.3.36	0.88	0
16.3.36	1.014	0
17.3.36	1.08	0
18.3.36	0.659	0.301
19.3.36	0.576	1.824
20.3.36	0.84	0.28
21.3.36	0.899	0
22.3.36	0.655	0
23.3.36	0.81	0
24.3.36	1.53	0
25.3.36	0.576	1.344
26.3.36	1.152	0.568
27.3.36	1.10	0.18
5.4.36—Operated		
30.4.36	1.305	0.405
1.5.36	1.44	0.201
2.5.36	1.08	0
3.5.36	1.286	0.255
4.5.36	1.08	0.532
5.5.36	0.99	0
6.5.36	0.823	0.124
7.5.36	1.282	0
21.6.36	0.765	0.35
22.6.36	0.90	0.21
23.6.36	1.191	0
24.6.36	1.65	0
25.6.36	1.02	0.284
26.6.36	0.94	0.25
27.6.36	0.88	0.11
28.6.36	1.31	0
19.3.36—5 gram. creatine per os (31 % eliminated)		
25.3.36—5 " " " (27 % ")		

Chromophobe adenoma. W., male. Aged 45. Weight 209 lb. Was admitted to the National Hospital, under the care of Dr. Critchley, complaining of headache and loss of vision. No skeletal changes were present.

X-ray of the skull showed an enlarged sella and erosion of the clinoid processes. The clinical diagnosis of chromophobe adenoma was confirmed by Dr. Greenfield, who reported on tissue removed at operation.

The results are tabulated below :

Date.	Creatinine gm./24 hr.	Creatine gm./24 hr.
10.5.36	1.31	0
11.5.36	1.05	0
12.5.36	1.0	0.15
13.5.36	0.86	0.20
14.5.36	1.45	0.20
15.5.36	0.9	0
16.5.36	1.32	0
17.5.36	1.05	0
18.5.36	1.51	0.30
19.5.36	1.60	0
20.5.36	0.96	0.30
21.5.36	1.15	0
22.5.36—Operated		
27.5.36	1.1	0.25
28.5.36	1.32	0
29.5.36	0.965	0
30.5.36	1.15	0
31.5.36	0.90	0.125
1.6.36	1.18	0.15
2.6.36	1.31	0
3.6.36	0.985	0
4.6.36	1.45	0
5.6.36	1.07	0.21
6.6.36	1.25	0.25
7.6.36	1.41	0.19
8.6.36	1.45	0

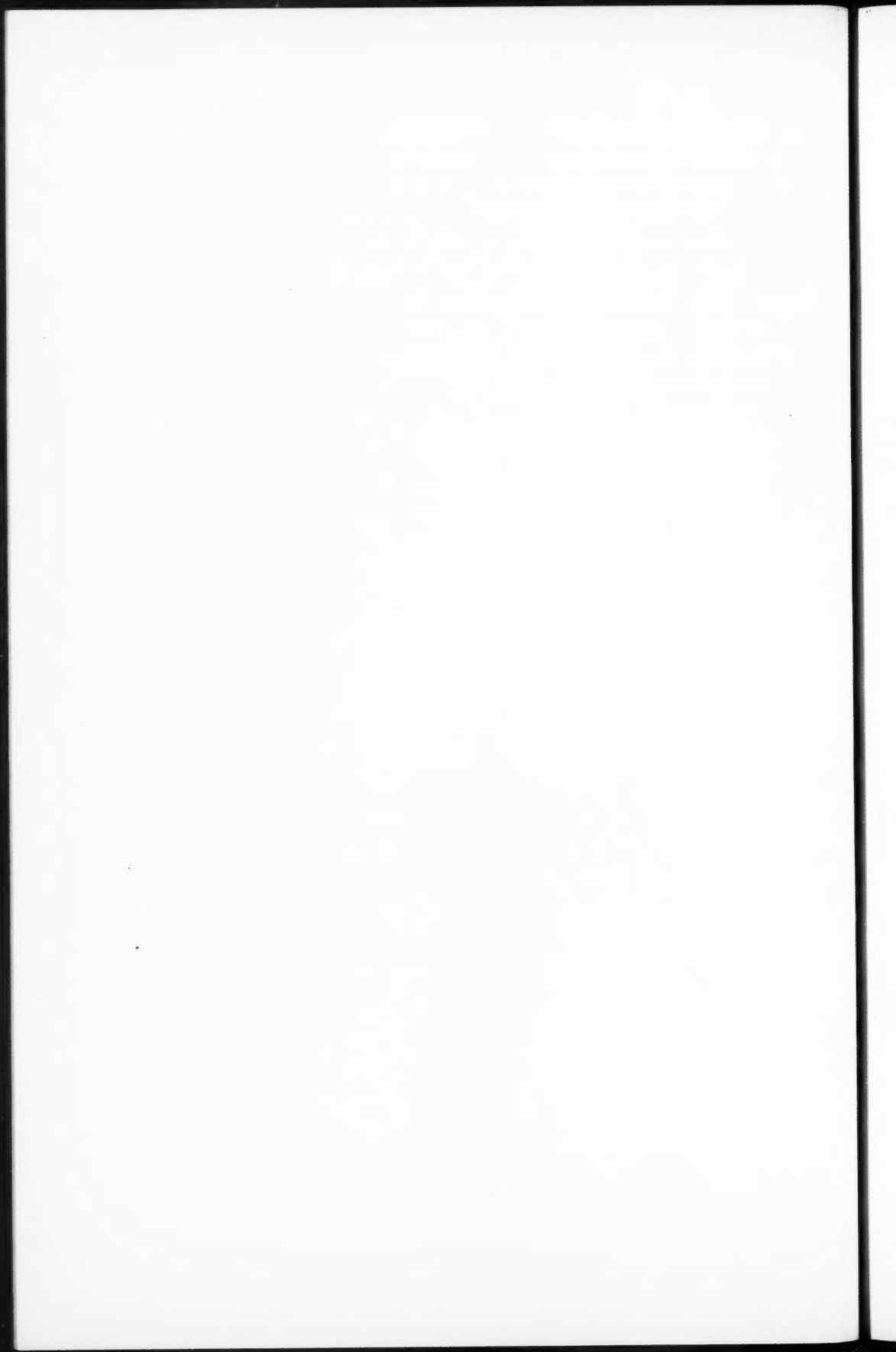
Chromophobe adenoma. P., male. Aged 30. Weight 151 lb. Was admitted to the National Hospital, under the care of Dr. C. P. Symonds, complaining of headache and loss of vision. The headache commenced one year previously and the visual disturbance had lasted three months. The fields of vision showed a loss of vision in both temporal fields. Both optic disks were pale. The skin of the body was of fine texture and the genitals were small. There were no skeletal changes. X-ray of the skull showed an enlarged sella turcica.

The results of the investigation are tabulated below :

Date.	Creatinine gm./24 hr.	Creatine gm./24 hr.
19.6.36	1.25	0
20.6.36	1.01	0
21.6.36	1.30	0.11
22.6.36	0.75	0.15
23.6.36	0.91	0
24.6.36	1.25	0.10
25.6.36	0.80	0
26.6.36	1.35	0
27.6.36	1.29	0.19
28.6.36	0.81	0.125

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OBSERVATIONS ON AGRANULOCYTOSIS¹

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THE first recorded case of agranulocytosis (or agranulocytic angina) was probably that of Brown and Ophüls in 1902 (5), but no particular attention seems to have been paid to the condition until Schultz (28) described a group of cases in 1922. Since that time many records of patients suffering from the disease have been published; recently fuller investigations into its nature have been carried out and clinical features established. Primary agranulocytosis appears to be a specific syndrome whose characteristic features are: 1. Sudden onset—usually a few days, rarely longer. 2. Lesions of the mouth, often notable for their insignificance in relation to the severity of the illness; bacteriological examination reveals organisms of no special aetiological significance. 3. Slight anaemia—red cells usually above $3\frac{1}{2}$ millions per c.mm. 4. Granulocytes very low or absent. 5. Absence of haemorrhages. 6. No enlargement of lymphatic glands—except when due to adjacent ulceration. 7. No, or at most very few, immature white cells in the circulating blood.

Many cases of granulopenia do not conform to these criteria, and the absence of granulocytes is then usually secondary to some other primary condition such as septicaemia, leukaemia, or aplastic anaemia.

Recent reviews of the work on this syndrome have been published by Adams (1), Jackson and Parker (16), and Stenn (31). Jackson and Parker were able to report 103 cases from their own records, and about the same time Plum (22) collected from the literature 128 cases of agranulocytosis caused by amidopyrin, and published an account of a further 7 of his own. Kracke and Parker (18) mentioned reports of 172 cases said to have been caused by drugs, of which 153 were possibly due to amidopyrin. In the last two years several further cases have been reported in this country (35).

On the whole the reports support the view that primary agranulocytosis is a specific syndrome with several aetiological factors. These factors seem to divide the cases into two broad groups.

A. Agranulocytosis Secondary to Toxic Substances

In this group the aetiological factor is some definite substance, usually used for therapeutic purposes, to which the patient shows an idiosyncrasy, or which has definite known toxic effects. Many drugs have been shown to

¹ Received September 26, 1936.

cause agranulocytosis. The commonest is amidopyrin, whose effect was first noticed by Madison and Squier (20); others include dinitrophenol and dinitrocresol used in the treatment of obesity, benzol, arsphenamine, bismuth, and gold salts (1, 16, 31); cases have also been reported after the use of drugs having a structure slightly different from amidopyrin, such as novaldin and novalgin (3, 11, 17).

Madison and Squier demonstrated that amidopyrin was the causal factor by giving to a patient who had recovered from agranulocytosis a therapeutic dose and producing thereby a sharp fall in the granulocytes with a recurrence of the subjective symptoms. Similar experiments have been reported by Plum (22), who gave details of three other reports. The results were explained by supposing that these patients showed an idiosyncrasy towards amidopyrin. Attempts to disclose this hypersensitivity by intradermal and similar tests have mostly been unsuccessful, but recently Dameshek and Colmes (7) claimed that the use of a mixture of a 5 per cent. aqueous solution of amidopyrin and blood-serum, which had been allowed to stand in the refrigerator for some days, gave a strongly positive intradermal reaction in patients who had previously had agranulocytosis; other forms of test were negative. Two of their patients actually developed attacks of agranulocytosis though the dose of amidopyrin used was only $\frac{1}{4}$ gr.

Several facts have been observed in connexion with agranulocytosis following drugs. It has been shown that a patient may develop agranulocytosis after amidopyrin has been taken for a considerable time without previous ill effects. Plum (22) states that 'it is an established fact that patients may suddenly have agranulocytosis after amidopyrin, even though they have used this drug previously without subjective discomfort'; Smith (30) reported a case (also seen by one of us) in which a man had taken $4\frac{1}{2}$ gr. daily for a year before developing frank agranulocytosis, though his condition had not been normal for some time; Holten and Hansen (14) produced depression of the granulocyte count by giving a therapeutic dose to a patient who had become sensitive after taking the drug regularly for two and a half years.

Olsen (21) has described a patient in whom, three years after an attack of agranulocytosis due to amidopyrin, another attack occurred after the exhibition of a relatively small dose of a gold salt. Benjamin and Biedermann (3) showed that a patient who was known to have agranulocytosis after amidopyrin also developed an attack after having been given a dose of a drug with a different but related structure. Von Bonsdorff (32), however, found that a patient who had developed agranulocytosis after arsphenamine was not sensitive to amidopyrin.

The frequency of amidopyrin hypersensitivity is not known. Rawls (24) reported the occurrence of four cases among 400 patients with arthritis who were having amidopyrin treatment; three of these cases were fatal. He thinks that the long-standing infection present in these patients might be responsible for this high frequency.

B. Idiopathic Agranulocytosis

No definite aetiological factor can be discovered in these cases.

After the reports of agranulocytosis following the use of the drugs mentioned above, it has been customary to inquire closely whether the patient had been taking drugs. Amidopyrin has been specially sought, since it formed an important constituent of many proprietary analgesics and patent medicines until the recent Poison Act in this country. A history of its use is often difficult to obtain, since patients do not look on these preparations, taken casually for headache, insomnia, or dysmenorrhoea—to mention the commonest conditions—as ‘medicine’.

Nevertheless, even after the closest investigation there remain some cases in which amidopyrin or other drugs have definitely not been taken. Jackson (15) stated that amidopyrin was the causal factor in only seven out of twenty-seven carefully studied cases, and he reported a case in which amidopyrin was given experimentally without deleterious effects. Plum (22) criticizes this statement on the grounds that the subject was not then of topical interest, and the question of amidopyrin may not have been pressed; he seems to suggest that a high proportion of the cases are due to amidopyrin poisoning. In the cases recently reported in this country some have been due to amidopyrin or similar drugs (36), but in those described by Castle-den (6), Fettes and Whitby (9), Lane (19), and in two of Hall's cases (12) no such aetiological factor could be detected. Reich (25) has reported a case following tonsillectomy where no amidopyrin had been given.

It has been suggested that in some of these cases of agranulocytosis without definite aetiology the diagnosis might have been at fault; in particular, confusion may have arisen with acute leukaemia. The distinction presents exceptional difficulties in cases in which the white-cell count is low and in aleukaemic leukaemia. Jackson and Parker (16) have pointed out that there are certain essential differences; ‘absence or marked diminution of platelets, anaemia of moment—particularly if progressive—haemorrhages, especially from the mucous membranes of the mouth; notable enlargement of the spleen and enlargement of the lymph nodes not readily explainable by adjacent ulceration and infection, all bespeak the diagnosis of acute leukaemia’, and they mention that any very considerable number of immature leucocytes is also in favour of leukaemia, irrespective of the total number of white cells.

The differentiation is particularly important since pentnucleotide therapy, which has been used successfully in agranulocytosis, is useless in acute leukaemia. Jackson and Parker mention some instances of reported failure with pentnucleotide that were not true cases of agranulocytosis.

More recent reports of the effect of pentnucleotide in indisputable cases of agranulocytosis have, however, been less favourable than earlier accounts. In Plum's series (*loc. cit.*) of cases due to amidopyrin, four out of five treated with pentnucleotide were fatal; others (37) have also reported failures.

Agranulocytosis seems, at least in this country, to be a rare condition. Only six true cases have come under our observation in two years (one reported already by G. S. Smith (30)), but, in addition, cases of persistent chronic neutropenia have been seen.

Case Reports

Case 1. A married woman, aged 54 years, was admitted to the Manchester Royal Infirmary on October 10, 1934, complaining of sore throat and prostration. The history was that early in July she was taken ill and collapsed quite suddenly; her throat became sore, there was swelling of the tongue and dysphagia. She was taken to a hospital, where some 'injections' (nature not ascertained) were given, and she recovered in a few days. She remained well until October 1, when she again became suddenly ill with shivering, sweating, and general malaise; her doctor reported that she had marked pyrexia. On October 6 she complained of sore throat, headaches, and vomiting, the bowels were constipated, and there was some nocturnal frequency of micturition. The menopause had occurred about four years previously. She said that she had lost 14 lb. in weight during the last three months.

Examination showed a fairly well-nourished woman with grey hair, dyed 'blonde'. Her colour was good and her cheeks flushed. The tongue was rather dry with a slight white fur. The tonsils were red and oedematous, with some small, shallow ulcers on the surface. The throat was red and oedematous, but not ulcerated. The mucous membrane of the mouth was very sore, and there was some exudate at the corners of the mouth. All the teeth had been removed eight years previously. The temperature was 101° F., the pulse rapid and regular, rate 112. In the abdomen the spleen was just palpable, the liver not enlarged. The other systems revealed no noteworthy features. There were no enlarged lymph glands, no rash, and no haemorrhages. The blood count showed: red cells, 4,080,000 per c.mm.; colour index, 0.92; haemoglobin, 74 per cent.; white cells, 2,100 per c.mm.; polymorphonuclears, 2.0 per cent.; lymphocytes, 94.75 per cent.; and monocytes, 3.25 per cent.

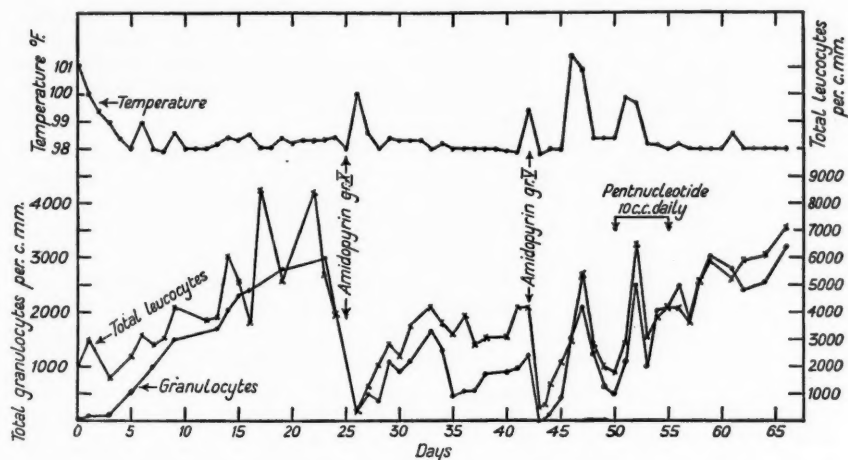
The patient was questioned about the use of drugs, and it was found that she occasionally took a proprietary mixture of barbitone and amidopyrin for insomnia.

The day after admission the temperature was lower, there was a slight increase in the number of granulocytes, and the patient felt better. No pentnucleotide was therefore given and, as will be seen from the chart, the temperature soon fell to more normal levels, while the granulocytes rose, though slowly; after fourteen days there were 5,100 white cells per c.mm., of which 45 per cent. were polymorphonuclears. Myelocytes were seen during this phase, but never more than 1 per cent.

In order to determine whether this was a case of amidopyrin idiosyncrasy it was decided to give a small dose of amidopyrin and to observe the effects. On November 3 the white-cell count was 3,900 per c.mm., with 51 per cent. polymorphonuclears. At 8 p.m. on the 4th, 10 gr. (0.6 grm.) of amidopyrin were given. Within an hour the patient felt unwell, and vomiting occurred during the night. Next morning the white-cell count was 400 per c.mm., with 49 per cent. granulocytes; the temperature rose to 100° F. Recovery set in almost at once, and was allowed to proceed without interference, no pentnu-

cleotide being given. On November 6 there were 1,300 white cells per c.mm. with 39 per cent. granulocytes, and, as the chart shows, recovery proceeded at roughly the same rate as before; neither the total white cells nor the granulocytes rose so high, and they became stabilized at a rather low level.

The first dose of amidopyrin had been given while the white cells seemed



to be diminishing. A further dose was therefore given when the white cells were more constant. On November 21 the white cells were 4,200 per c.mm., with 28.5 per cent. polymorphonuclears. At 8 p.m. 5 gr. (0.3 gm.) of amidopyrin were given. Twenty minutes later the patient complained of nausea and vomited. During the night she complained of headache, and there was some pyrexia. Next morning the white-cell count was 500 per c.mm., and no granulocytes could be found in stained films; at 5 p.m. on the same day there were 700 white cells per c.mm. and only 1 per cent. granulocytes, while on the following morning there were 1,400 white cells with 9 per cent. granulocytes. Recovery seemed to be proceeding as before, and it was decided to try to accelerate the rate of increase of the granulocytes by giving pentnucleotide. Before this treatment was started the patient again showed a rise of temperature, probably due to some infection which, as the chart shows, lasted three days. This pyrexia was accompanied by a sharp rise in total leucocytes and in granulocytes; on the second day of this pyrexial attack there were 5,400 white cells per c.mm. and 39 per cent. polymorphonuclears. When the pyrexia had subsided the white cells and the granulocytes fell almost to their previous levels, being 1,800 per c.mm. and 29.5 per cent., respectively, five days after the onset. Pentnucleotide therapy was now commenced, 10 c.c. being given intramuscularly daily for seven days. There was a sharp rise in granulocytes and in total white cells, but as this was accompanied by another rise in temperature it is doubtful whether this was due to the pentnucleotide, especially as the counts fell when the temperature became normal. On the whole, the chart shows that there was very little difference between the general rate of recovery when pentnucleotide was given and that when it was withheld.

The patient improved steadily, and she was discharged to the departmental out-patient clinic with a count of 4,700 white cells per c.mm. and 43 per cent. granulocytes.

She was warned against taking drugs and the nature of her condition explained to her. She remained under observation for eight months, during which time there was no recurrence and the white cells remained between 3,000 and 5,000 per c.mm. with about 50 to 60 per cent. granulocytes.

This was a case of agranulocytosis due to idiosyncrasy to amidopyrin; the aetiology was proved by trial doses, and it appeared that recovery was spontaneous and not much influenced by pentnucleotide. The fact that she had apparently taken amidopyrin before without symptoms is in conformity with the observations of others.

Case 2. In 1934 we (33) described a case of agranulocytosis which responded well to pentnucleotide therapy. This was a woman, aged 34 years, who became suddenly ill with dysphagia, cough, and painful swellings below the jaw. Later there were severe general symptoms with rigors, a rash of septic spots appeared on both hands and on the gums and mucous membrane of the mouth. Five days after the onset she was admitted to hospital and the blood count showed: red cells, 3,690,000 per c.mm.; haemoglobin, 76 per cent.; colour index, 1.02; white cells, 1,000 per c.mm.; polymorphonuclears, nil; lymphocytes, 97 per cent.; monocytes, nil; Türk cells, 3 per cent.

Examination of a swab from the throat showed a few streptococci and on culture a small growth of non-haemolytic streptococci was obtained. An initial dose of 40 c.c. of pentnucleotide was given intramuscularly, followed by 20 c.c. daily for four days and then three daily doses of 10 c.c. On the fourth day the granulocytes had risen to 1,380 per c.mm. and on the eighth day there were 9,400 white cells per c.mm. and 53 per cent. polymorphonuclears; the clinical condition was greatly improved and the septic spots had disappeared. During the recovery period myelocytes appeared and rose to 8 per cent. (545 per c.mm.) on the fourth day.

The case is mentioned again because the most careful subsequent investigation failed to reveal any history of amidopyrin having been taken, and because of the after-history. Three months after leaving hospital she became pregnant; the blood was examined periodically throughout and pregnancy, labour, and the puerperium were carried through without any haematological complications. Roberts and Kracke (26) have said that none of their recovered cases returned to complete health; Jackson and Parker (16) doubt the accuracy of this statement and mention some of their cases where recovery was apparently complete. The case reported here supports the contention of Jackson and Parker.

Case 3. A married woman, aged 48 years, was admitted to the Manchester Royal Infirmary on June 29, 1935. The history was that about a week previously she had complained of a severe sore throat and a feeling of extreme weakness. She rapidly deteriorated and became seriously ill. Examination had shown swelling and oedema of the soft palate and sloughs on both fauces; the temperature was raised. A bacteriological examination of the throat had shown that no diphtheria organisms were present.

When admitted to the infirmary she was severely ill and comatose, the temperature was 104° F., the pulse was running in character, rate 128, and respirations were 40 per minute. There was severe swelling and oedema of the soft palate and over the back of the tongue and spreading on to both

fauces there was an area of blackish discoloration with small, well-defined ulcers having yellow bases. The spleen was not palpable, the liver was not enlarged, there were no enlarged lymph glands. No haemorrhages had occurred.

The blood count was: red cells, 4,384,000 per c.mm.; haemoglobin, 74 per cent.; colour index, 0.86; white cells, 500 per c.mm.; polymorphonuclears, 44 per cent.; lymphocytes, 80 per cent.; monocytes, 7 per cent.; Türk cells, 9 per cent. Platelets were fairly abundant.

So far as could be ascertained, there was no history of her having taken any amidopyrin or other drugs.

The patient died very shortly after admission, before any treatment could be given.

Post-mortem examination (by Dr. Davson).

There were no petechiae on the body. The posterior third of the tongue was the seat of widespread congestion with thickened discoloured areas at the sides and several sharply defined ulcers with yellow necrotic floors. The upper surface of the epiglottis and its posterior surface and the surface of the arytenoid cartilages showed similar congestion, blackish discoloration, and ulceration. Destruction was mainly superficial. The larynx itself was unaffected, as was the trachea. The lungs were congested and oedematous. The dilated heart showed a pale myocardium, and a few minute fibrinous vegetations were seen on the cusps of the aortic valves. The oesophagus was healthy, the stomach showed some congestion, the intestines were also healthy. The liver (1,500 gm.) showed the uniform smoky-pink appearance of cloudy swelling. The spleen (200 gm.) was enlarged and soft; the pulp was dark purple in colour, and friable. The kidneys showed cloudy swelling and congestion. There was some enlargement of the thyroid gland. The femoral bone marrow was red and hyperplastic.

Microscopical examination. Bone marrow: some cellular hyperplasia between the fat spaces, but these spaces were not at all obscured. The cellular content was notable for the almost complete absence of polymorphonuclears; of the myelocytes only an occasional basophil was seen, and no other types. The cells were chiefly small round cells with a sprinkling of erythroblasts, myeloblasts, and megakaryocytes. Collections of red cells occurred everywhere.

Spleen: the pulp was cellular, but the Malpighian bodies much smaller than normal. There were only few polymorphonuclears among the pulp cells.

Liver: some small areas of fatty change at the lobular peripheries were seen.

This case is an example of the very acute and fatal type, apparently not associated with amidopyrin.

Case 4. A housewife, aged 66 years, had been troubled for some twelve months with bronchitis and pulmonary fibrosis, but there was no evidence of tuberculosis. She suffered a great deal from headaches, for which she frequently took a certain proprietary headache powder, but the relatives could not assess the total amount taken.

For some weeks prior to being seen by one of us she had been feeling a little off colour. On August 8, 1936, she suddenly felt ill and had a rigor, but there was no cough or sore throat; her temperature rose to 103° F. and the pulse was 100. A few hours later the pharynx and tonsils appeared to be congested and sensitive, although free from exudate or ulceration. The following day she complained of severe pain in the throat and discomfort

on breathing; there was an area of blackish-grey membranous exudate adherent to the tonsils. The general condition did not show any improvement and the cervical and tonsillar glands became enlarged and tender; the tissues of the neck were brawny and indurated.

The patient was now severely prostrated, with a marked pyrexia, sore throat, oedema and ulceration of the pharynx, tonsils, and mouth, without any evidence of reaction. She was edentulous. There was no obvious loss of weight.

By this time the temperature had fallen to 98° F. and there were moist sounds at the bases of both lungs; the cardiac sounds were very weak, the heart was slightly dilated, and the pulse was rapid and regular. The spleen and liver were not enlarged, and only the lymphatic glands of the cervical region were enlarged. The nervous reflexes were present and practically normal.

An enema had returned dark tarry motions, but apart from this there was no evidence of haemorrhage. Bacteriological examination of throat swabs did not show any diphtheria bacilli, haemolytic streptococci, or micro-organisms of Vincent's angina.

A partial blood examination showed red cells, 4,400,000; white cells, 360; while only lymphocytes and no granular cells were seen in the stained film. A further examination some fourteen hours later showed a total white-cell count of 130 per c.mm. with a differential count of: lymphocytes, 86 per cent.; large mononuclears, 8 per cent.; Türk cells, 6 per cent.; abundant platelets and marked anisocytosis and poikilocytosis.

In view of the severity of the patient's condition she was given at once 10 c.c. of pentnucleotide intramuscularly, followed by two doses of 20 c.c. intravenously and 10 c.c. intramuscularly six, nine, and twelve hours later, respectively. The patient was then in a very poor condition, and she died the same day. Unfortunately no autopsy was obtained.

This was certainly a case of acute fulminating agranulocytosis, probably secondary to amidopyrin taken in small quantities in a headache powder. The whole duration of the condition was apparently only two or three days.

Case 5. A bricklayer, aged 44 years, was admitted to hospital on January 30, 1936. In July 1935 he had been hit in the lower dorsal region of the spine while at work. Since that time he had complained of pain in the affected region and in both iliac fossae of sufficient severity to prevent his working. No definite injury was found, and an X-ray examination revealed only an old scoliosis. In November he had a 'septic mouth'; he was slightly jaundiced, there was pyrexia—up to 105° F.—and the spleen was very tender. This condition had never cleared up, the jaundice and the stomatitis persisting. The patient had lost his appetite and complained of nausea and some loss of weight.

On examination the patient was seen to be a well-nourished man of dark complexion with a slight yellow tinge in the face and neck. The conjunctivae showed no icterus. The tongue was moist and furred. There were small whitish ulcers on the upper gum of both sides and on the hard palate; the tonsils were enlarged but not ulcerated, the throat appeared red but also showed no ulcers. There were no upper teeth, and the lower ones seemed in fair condition. Neither petechial haemorrhages nor enlarged lymph glands were found. In the abdomen there was some tenderness in both hypochondria but no abnormal mass was palpated, the spleen was not palpable, and the liver not enlarged. Rectal examination revealed a fistula-

in-ano. Examination of the other systems revealed nothing of particular note, and there was no evidence of injury to the spine. The blood count showed: red cells, 3,810,000 per c.mm.; haemoglobin, 72 per cent.; colour index, 0.94; white cells, 5,300 per c.mm.; polymorphonuclears, 4 per cent.; lymphocytes, 87.5 per cent.; monocytes, 8.5 per cent.; no other forms of white cells; platelets scanty.

Case 5. Table of Blood Counts.

Date.	White cells, per c.mm.	Poly-morphs., %	Lympho-cytes, %	Mono-cytes, %	Türk cells, %	Pent-nucleotide dose.
1936						
31 Jan.	5,300	4.0	87.5	8.5	0	nil
2 Feb.	5,200	0	83.5	15.5	1.0	nil
3 "	4,400	2.0	82.5	15.5	0	20 c.c.
4 "	3,600	1.0	75.5	23.5	0	30 c.c.
5 "	3,500	0	75.5	21.0	3.5	30 c.c.
6 "	2,300	0	70.25	27.75	2.0	nil
7 ", *	2,400	0.25	54.0	42.75	3.0	30 c.c.
8 "	3,200	0	49.0	49.0	2.0	50 c.c.

* On February 7 the red cells were 3,650,000 per c.mm.; haemoglobin, 70 per cent.; colour index, 0.96.

Bacteriological examination of a throat swab did not disclose any noteworthy infection.

The patient had had several tablets from his doctor for relief of pain, but these did not contain amidopyrin.

Treatment with pentnucleotide was commenced on February 3, 20 c.c. being given intramuscularly on this day and 30 c.c. on each of the following two days.

The blood condition, as the table shows, did not respond at all, and the clinical condition of the patient seemed to be worse although the ulceration in the mouth did not progress further. After an interval of one day, therefore, a further 30 c.c. were given, and on the next day, as the patient's condition was grave, 20 c.c. were given intramuscularly and 30 c.c. intravenously. This had no effect and the patient died on February 9.

Post-mortem examination (by Dr. Davson).

The body was rather yellowish in colour. There was no external evidence of injury. The mucous membrane of the tongue was healthy, but there was a small ulcer at the margin of the right upper gum with a necrotic base. The pharynx and larynx were injected but not ulcerated; the trachea was congested. The lungs showed severe oedema and congestion. The heart was small with a rather flabby myocardium; the valves were healthy. In the oesophagus the lower half was completely covered by a greenish-yellow exudate which was adherent, and when removed exposed shallow ulcerated areas. The stomach showed marked post-mortem discoloration; the intestines were healthy. The liver (2,100 grm.) was enlarged, of a uniform pinkish-brown colour, and was soft and greasy. The gall-bladder contained 'white bile', but there was no organic obstruction of the ducts. The spleen (240 grm.) was enlarged, the pulp was firm and dark red in colour; the Malpighian bodies were not obvious. The pancreas appeared healthy. The kidneys were rather large (200 grm.), but their pattern was clearly marked. The bone-marrow of the femur was orange or yellow in colour with pinkish

areas: it was easily lifted from the marrow cavity. The vertebral marrow was red. No injury to the spine was found.

Microscopical examination. Femoral bone-marrow: only a few cells were present between the fat spaces; the majority of these were lymphocytes and normoblasts, there were very few 'blast' cells and a very rare degenerate polymorphonuclear.

Vertebral marrow: cellular, mostly lymphocytes; a few 'blast' cells were seen; granular leucocytes were almost entirely absent.

Spleen: Malpighian bodies normal, the pulp was rather haemorrhagic; hardly any granular leucocytes were seen in the pulp.

Liver: appeared healthy apart from some cloudy swelling.

Oesophagus: mucous membrane very necrotic and ulcerated but the cellular reaction was not marked and very few polymorphonuclears were found.

This case was notable for the relatively slow onset, the increasing proportion of monocytes in the blood, the failure of pentnucleotide to evoke any response, and the ulceration of the oesophagus.

Case 6. A married woman, aged 48 years, first attended the departmental out-patient clinic on November 8, 1934. The history was that for the previous two years she had been troubled with headaches and backache. About four weeks previously she had had pain in the left hypochondrium, of a burning character, appearing in 'attacks' lasting from two to three minutes. She also stated that for some months she had felt very tired and disinclined to carry on her housework, and her relations agreed that this was abnormal. No sore throat had occurred, and neither rashes nor haemorrhages had been seen. There were numerous complaints of a very vague character. The bowels were occasionally constipated, there was some nocturnal frequency of micturition, menstruation was regular but becoming scanty. No treatment had been given apart from aspirin.

Examination showed a well-nourished, obese, rather pale woman. Mouth, throat, and tonsils appeared healthy; the tongue was furred and moist, her teeth were artificial. The temperature was normal, the pulse fairly full and regular, rate 100. The spleen was not palpable, and there was no enlargement of the liver and lymph glands. The heart was of normal size, the blood-pressure 140/80 mm. No unusual features were detected in the other systems.

The blood count was: red cells, 3,800,000 per c.mm.; haemoglobin, 74 per cent.; colour index, 0.98; white cells, 1,800 per c.mm.; polymorphonuclears, 10 per cent.; lymphocytes, 88 per cent.; monocytes, 2 per cent.

She was admitted to the Manchester Royal Infirmary one week later for investigation. The white-cell count was then 900 per c.mm. with 10 per cent. granulocytes. Fractional gastric analysis showed a high normal curve. The electrocardiogram was of rather low voltage but no irregularities were found; this was done because the house physician noticed that during the attacks of pain the pulse-rate rose to 144, but he could not detect any irregularity.

In view of the low granulocyte count, a course of pentnucleotide treatment was given. The table of blood counts shows that there was a definite rise in the granulocytes, and the total white cells were about doubled, but the reaction was slow and no myelocytes appeared. After 80 c.c. had been given the treatment was stopped as the patient now complained that the injections were causing her much pain. The granulocytes fell almost at once to their former level. She was discharged to the out-patient clinic

shortly afterwards and kept under observation. The table shows that her granulocytes remained at a uniformly low level. No sore throat or other similar affection occurred. Menstrual irregularities were troublesome, and the patient continued to complain of great fatigue, which did not yield to treatment of any sort. The abdominal pains had ceased.

Case 6. Table of Blood Counts.

Date.	Red cells, per c.mm. × 10 ⁶ .	Hb. %	White cells, per c.mm.	Poly- morphs., %	Granulo- cytes, per c.mm.	Treatment.
1934						
25 Oct.	3.80	74	1,800	10.0	180	—
15 Nov.	3.23	65	900	10.0	90	—
17 "	—	—	1,200	5.0	60	—
19 "	—	—	1,300	10.0	130	20 c.c. pentnucleotide
20 "	—	—	1,100	17.5	192	10 " "
21 "	—	—	1,400	19.0	266	10 " "
22 "	—	—	1,600	19.0	304	10 " "
23 "	—	—	1,660	15.0	240	10 " "
24 "	—	—	1,700	17.0	289	10 " "
25 "	—	—	1,800	16.0	288	10 " "
26 "	—	—	1,900	22.0	418	—
27 "	—	—	2,600	23.0	598	—
29 "	—	—	1,500	12.0	220	—
30 "	—	—	1,300	12.0	156	—
3 Dec.	—	—	500	6.0	30	—
6 "	3.95	66	1,200	12.0	144	Iron therapy
20 "	—	—	1,700	9.0	170	"
1935						
17 Jan.	4.29	74	1,300	13.5	182	"
14 Feb.	4.10	76	1,200	9.0	108	"
14 Mar.	4.61	73	1,100	11.0	121	"
25 Apr.	3.67	66	1,600	12.0	208	Iron therapy
6 June	3.92	82	2,000	15.0	300	"
18 July	4.53	78	1,600	17.0	280	"
23 Sept.	4.16	78	2,100	30.5	640	—
25 Oct.	4.00	68	800	15.0	120	—
28 Nov.	4.11	70	1,800	8.0	124	Iron therapy

*Granulocytes' includes polymorphonuclears, eosinophils, and basophils.

On September 23, 1935, there was a recurrence of the abdominal pain accompanied by some vomiting. The white cells were low, as before. She was re-admitted, but investigation failed to show any organic abnormality. Treatment with oestrin was commenced for menopausal symptoms and the patient states that she now feels somewhat improved; nevertheless, the granulocytes still maintain a subnormal level and the patient declines further treatment with pentnucleotide.

This case corresponds with the 'subchronic type' of Beck's (2) classification. Two similar cases were described by Rosenthal (27) where there was also a continuous leucopenia of about 1,500 per c.mm., and easy fatigue was the prominent symptom; they had been under his observation for six years and their condition was more or less unaltered.

The granulocytes in our case showed a prolonged and extreme depression never rising above 640 per c.mm. (30.5 per cent.), and it must be emphasized that it is only this state that deserves the name 'chronic neutropenia': it is undesirable that the term should be applied to any condition accompanied by only mild depression of the granulocytes, as such depressions are almost exclusively secondary in character and do not represent the true granulopenic syndrome.

Discussion

The cases reported here support the idea that agranulocytosis is a specific syndrome primarily due to disturbance of the granulocyte-forming tissues and characterized by suddenness of onset and a severe and rapid clinical course with, as a rule, relatively unimportant lesions in the mouth and throat. There appear to be 'idiopathic' cases as well as those in which the aetiological factor is a known toxic drug. Although the onset is usually sudden, there is often a history of some weeks of vague ill health.

The effect of amidopyrin on the granulocytes observed in Case 1 is notable for the rapidity with which the granulocytes disappeared from the circulating blood and the quick return of the symptoms. This is in agreement with the observations of others (*vide supra*) and supports the view that the condition is due to idiosyncrasy. It is possible that some unsuspected factor acting in a similar manner is the cause of the condition in those cases that at present are termed 'idiopathic'.

The changes observed in the bone-marrow are also in agreement with the hypothesis that the effect is specifically on the granulocyte-producing tissue. Plum (23) examined the sternal marrow in three susceptible cases before and after the administration of amidopyrin, and found that there was a protracted inhibition of granulocyte formation affecting myelocytes and promyelocytes as well as polymorphonuclear cells. Autopsy findings show an almost complete absence of polymorphonuclears and other granular cells; the number of myeloblasts varies with the duration of the illness as Darling, Parker, and Jackson (8) have pointed out; the longer the clinical course, the smaller the number of myeloblasts, which become replaced by plasma cells and lymphocytes.

In chronic neutropenia the same syndrome of prolonged and inexplicable lassitude and vague malaise seems to have been noted in all the recorded cases. The number of cases, however, is not large enough, nor the features of the syndrome sufficiently clear to make it certain whether the neutropenia is primary or only an associated condition.

With regard to therapeutics, it has been found, in agreement with recent reports, that pentnucleotide has not been so successful as had been hoped; the records of Case 1 suggest that it may have little effect on the rate of recovery of some cases, and in Case 5 reasonably prolonged administration failed to evoke any response. Nevertheless, it is the only form of treatment that has led to a reduction of the mortality of agranulocytosis, and should always be given as early as possible. Pentnucleotide seems to be of little use in chronic neutropenia, having little effect on the granulocytes or on the clinical condition of the patient.

Summary

1. Four cases of agranulocytosis and one of chronic neutropenia are described; the subsequent course of a previously reported case is also given.

2. Amidopyrin was the aetiological factor in two cases, one of which was fatal: in the non-fatal case this was proved by giving a therapeutic dose which caused a sudden reduction of the granulocytes to extremely low levels and the return of the symptoms.

3. No aetiological agent was discovered in the other cases.

4. Three cases of agranulocytosis were fatal; the haemopoietic tissues were examined in two of them and showed an almost complete absence of granular leucocytes, though the cells of the other series were not diminished.

5. Pentnucleotide was given to five patients. In the non-fatal amidopyrin case it appeared not to increase the rate of recovery of the granular leucocytes, and in the fatal cases no response at all was evoked; the second case responded well to this treatment. It caused a small transient increase in the granular leucocytes in the patient with chronic neutropenia, but did not influence the clinical condition.

6. Ulceration of the oesophagus was found in one case.

This work formed part of an investigation on behalf of the Therapeutic Trials Committee of the Medical Research Council into the value of pentnucleotide in the treatment of agranulocytosis.

We gratefully acknowledge assistance we have received from the Medical Research Council and the Lady Tata Memorial Trust, and also from Messrs. Menley and James who supplied the pentnucleotide used in this work.

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THE PROGNOSIS FOLLOWING RECOVERY FROM CORONARY THROMBOSIS, WITH SPECIAL REFERENCE TO THE INFLUENCE OF HYPERTENSION AND CARDIAC ENLARGEMENT¹

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THE widespread recognition of coronary thrombosis is still so recent that knowledge regarding the after-history is only beginning to accumulate. Two years ago it was suggested at a discussion at the Royal Society of Medicine that the whole subject of prognosis could not yet be approached with full confidence (3). Until sufficient time has elapsed for large series to be followed to necropsy our knowledge must be inexact, but pending this, a utilization of the available clinical material as a working basis is permissible.

The present communication comprises an analysis of 212 case histories of patients known to have survived a first attack by at least three months. They were assembled from the Cardiac Department of the London Hospital and from a consulting practice; any in which the clinical diagnosis was in any doubt were rejected. Seventy-three per cent. formed a hypertensive group which included all those ever found, whether prior or subsequent to the attack, to have blood-pressure readings at or higher than 160 mm. systolic and/or 100 mm. diastolic (7). In 200 the size of the heart was determined by radiological methods; enlargement was found in 64 per cent., by far the most important cause being hypertension (8). Discussion in the present paper will be chiefly concerned with the influence exerted after the attack by hypertension as such, and by cardiac enlargement, and it will be shown that while hypertension may be neglected in so far as its effect on the prognosis is concerned, enlargement is of prime importance.

Capacity for exertion. One hundred and eighty-eight patients, observed for an average period of 4.9 years, each of whom had been followed for at least a year after the attack, were classified into two groups, active and restricted. The former consisted of those able to lead a life considered to be almost normal for their ages; the latter, of those whose activities were definitely restricted, including the invalids and semi-invalids. The line of demarcation between active and restricted cannot be sharply defined, and about half of those in the active group were subject to slight pain or dyspnoea during more than normal activity. Furthermore, the absence of a common standard for

¹ Received September 14, 1936.

defining normal activity made it necessary to decide each case on its own merits; a business man able to carry on his business and play golf was classified as active along with the manual labourer who was able to return to work that did not require maximum exertion.

Fifty-five cases (29 per cent.) fell into the active group, and 133 (71 per cent.), including 15 invalids, into the restricted. The percentage of hypertensives was the same in each group, and there was roughly the same proportion of cases with systolic readings of more than 200; the restricted group contained an almost 20 per cent. higher proportion of cases of cardiac enlargement (Table I).

TABLE I

Incidence of Hypertension and Cardiac Enlargement in Active and Restricted Groups of Patients Recovered from Coronary Thrombosis.

	Number of cases.	Hypertension.		Enlargement.	
		Number.	%	Number.	%
Active group	55	40	72.7	27*	51.9
Restricted group	133	97	72.9	89†	70.1
Angina pectoris as sole cause of restriction	52	35	67.3	28	54
Dyspnoea as sole cause of restriction	43	34	79	38‡	90.5

* Not including 3 cases where size unknown.

† Not including 6 cases where size unknown.

‡ Not including 1 case where size unknown.

Angina pectoris and dyspnoea on exertion were the principal causes of disability, the former having been found to be the only outstanding factor in 52 (39 per cent. of the restricted group), and the latter in 43 (32 per cent.). In addition there were 12 cases where both symptoms were equally prominent. While in the dyspnoeic group the percentage incidence of hypertension was only slightly higher than in the anginal group, that of cardiac enlargement was about 40 per cent. higher.

Other conditions found to be factors in causing restriction may be briefly mentioned. Intermittent claudication was the sole cause in 7, and was combined with angina or dyspnoea in 5 others. Exhaustion was a contributory factor in 7, chronic bronchitis in 8, bronchial asthma in 1, paroxysmal auricular fibrillation in 4. Two patients had frequent Stokes-Adams attacks. Hemiplegia, arthritis, and prostatism were the main causes of invalidism in 3 cases.

Angina pectoris. In 83 cases, 39 per cent. of the whole series, angina of effort was present for an average period of 2.3 years prior to the attack; about half of these had had it for less than a year. Subsequent to the attack it was found in 123 (58 per cent.): of this number 64 had had it previously and 59 had not. In 19 patients in whom pain did *not* recur following the attack, it could not be shown that the loss of angina was the result of a fall in blood-pressure; this was observed in several to become higher as the years went by, and in two the final level was actually higher than it was known to have been before the attack. Only 5 of the 19, 2 of

them hypertensives, were able to lead active lives, the common cause of disability in the others being dyspnoea. As will be shown later, it is significant that 4 of these 5 had normal-sized hearts, while in the remaining 14 there were 10 cases of enlargement, the size being unknown in the other 4.

The incidence of hypertension and of cardiac enlargement in the anginal group were roughly the same as in the whole series (cf. also Tables VII and VIII).

In 18 patients in the group the pain was mild enough in degree to permit them to be classified as active.

Age appeared to have no influence on the percentage incidence of angina, for it was found almost equally often in the fifth, sixth, seventh, and eighth decades.

Subsequent attacks of coronary thrombosis. In 59 cases (27.8 per cent.) of the 212 cases in the series, a second attack of coronary thrombosis occurred, in 11 (5.2 per cent.) a third, and in 2 (0.9 per cent.) a fourth. The distribution of these attacks by years is shown in Table II; it is seen that almost half of them were within two years of the original attack. The incidence of hypertension in the group was the same as for the whole series; that of cardiac enlargement rather higher, 70.4 per cent. as against 64 per cent. (cf. Table VI).

TABLE II

Incidence of Subsequent Attacks of Coronary Thrombosis in a Series of 212 Patients Surviving the First Attack by Three Months.

	Year subsequent to first attack.												Total.	Percentage of whole series.
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th		
2nd attack	15	16	4	10	5	2	2	2	2	—	—	—	59	27.9
Fatal	1	4	1	1	2	1	—	—	1	—	—	—	—	—
3rd attack	3	—	1	1	1	2	1	3	—	—	—	—	12	5.2
Fatal	1	—	1	—	—	—	1	—	—	—	—	—	—	—
4th attack	—	—	—	—	—	—	—	2	1	—	—	—	3	1.4
Total attacks	18	16	5	11	6	4	3	6	3	—	—	1	73	—

Thirty of the group are known to have died. In 14 death followed shortly after the new attack (second attack in 11, and third in 3), and was directly attributed to it; the average length of life in these cases subsequent to the original attack was four years, only 5 having died before the end of the second year. Six others finally died of congestive heart failure, and one in a Stokes-Adams attack. Three died non-cardiac deaths, and in 5 the cause of death was unknown.

Congestive failure. Gross congestive heart failure subsequent to the attack occurred in 27 cases (13 per cent.) Evanescient signs of failure are not uncommonly found during the first month following the attack in severe cases; only two are included in this group in which the onset was during this period, and in both of them the signs persisted for months. The average length of time elapsing between the onset of the attack and the appearance

of failure was 1·6 years, the longest such period being 7·5 years; in 12 cases failure set in within six months of the attack. The average duration of life following the onset of failure was 2·4 years.

Twenty-four cases (90 per cent.) were hypertensives, a proportion considerably higher than that for the whole series. Cardiac enlargement was found in 25, 100 per cent. of those examined by X-ray. The significance of these findings will be discussed later, when it will be seen that the higher incidence of hypertension is of importance only as an indication of a higher incidence of cardiac enlargement. Paroxysmal nocturnal dyspnoea, in addition to its occurrence in some of the above cases, was found in 8 others presenting both hypertension and enlargement. These clinical findings are in complete agreement with the necropsy evidence of Nemet and Gross (6), that 'chronic congestive failure in arteriosclerotic disease is overwhelmingly the failure of the hypertrophied heart'.

Fourteen of the cases of failure showed the following disturbances of rhythm or conduction: auricular fibrillation in 3, permanent since the attack in 1 and paroxysmal in 2; paroxysmal auricular flutter in 3; intraventricular block in 7; bundle branch-block in 2; temporary auriculo-ventricular block in 1.

Three cases had experienced failure at some time prior to the attack. Aortic stenosis was present in one case.

Duration of life following attack. The dispersal of the whole series is shown in Table III. One hundred and two cases (48·1 per cent.) are still under observation at the time of writing, while 45 (21·2 per cent.) have been untraced, almost two-thirds of them disappearing during the first two years of observation. Sixty-five (30·7 per cent.) are known to have died; their average duration of life from the onset of the attack was 4·3 years.

A statistical examination of Table III led to the conclusion that the rate of survival is probably considerably better than has been heretofore believed, and that of patients of all age groups who have lived for at least three months following a first attack of coronary thrombosis, almost 75 per cent. may be expected to survive to the end of the fifth year following the attack, and almost 40 per cent. to the end of the tenth year (Table IV). The average death rate from year to year during the first five years is about 6 per cent., and during the next five years about 12 per cent.

Table V shows the duration of life in various subdivisions of the whole series and of the mortal group. The figures for the whole series show of course merely the length of time during which the patients are *known* to have been alive. Whether they may be used as a source of information concerning the relative effect of various factors on the prognosis is for obvious reasons open to question, although they did run fairly parallel to those obtained in the same manner from the group of patients known to have died. While the group by itself cannot be made a basis for statistical analysis, general impressions formed as a result of study of the two groups of figures taken together are worthy of consideration.

TABLE III

Showing Dispersal of Series of 212 Cases of Coronary Thrombosis which Survived the Attack by Three Months.

Year following attack.	Died during observation period.	Lost trace of during observation period.	Surviving at time of writing, but observation period ended.*	Remainder under observation at end of each year following attack.
1st year	5	14	5	188
2nd "	9	14	11	154
3rd "	14	2	12	128
4th "	4	7	15	100
5th "	8	2	20	70
6th "	3	3	6	58
7th "	13	—	6	39
8th "	3	2	7	27
9th "	2	—	9	16
10th "	2	—	3	11
11th "	1	—	5	5
12th "	—	1	—	4
13th "	—	—	1	3
14th "	1	—	—	2
17th "	—	—	1	1
22nd "	—	—	1	0
Totals	65 (30.7 %)	45 (21.2 %)	102 (48.1 %)	

* Figures in this column indicate therefore patients who sustained attacks during each year in the past (dating back from the time of writing), and are known to be now alive.

TABLE IV

Yearly Rate of Survival, per 10,000, of Cases of Coronary Thrombosis which had Already Lived for Three Months Following a First Attack, Based on Experience of 212 Cases.

Years following first attack of coronary thrombosis.	Number of cases surviving out of 10,000.	Percentage surviving from year to year. %
0	10,000	100
1	9,753	97.5
2	9,253	94.9
3	8,372	90.5
4	8,081	96.5
5	7,354	91.0
6	7,017	95.4
7	5,359	76.3
8	4,893	91.3
9	4,458	91.1
10	3,843	86.2

In the hypertensive group the prognosis seems to be better than in those with normal blood-pressure; possible reasons for this are discussed later. The average length of life is somewhat curtailed in the group with enlarged hearts and in that with congestive failure, but is unaffected by angina pectoris or by further attacks of coronary thrombosis.

Out of the 34 in which the cause of death was known, 25 cases (73.5 per

TABLE V

Showing Average Duration of Life in Years from Onset of Coronary Thrombosis to End of Period of Observation.

	Entire series.		Known dead.	
	Cases.	Average duration to death or last observation.	Cases.	Average duration to death.
Total number of cases	212	4.15	65	4.3
Age groups: below 50	38	4.42	12	3.23
50-59	93	4.29	25	5.15
60-69	63	3.88	22	4.2
70 and over	18	2.93	6	3.32
All hypertensives	155	4.32	48	4.57
Hypertensives (200 mm. Hg and over)	43	4.41	18	5.14
Non-hypertensives	57	3.7	17	3.5
Cardiac enlargement	128	4.04	46	4.3
Normal sized heart	72	4.57	12	4.43
Congestive failure	27	4.04	20	3.88
Angina of effort	123	4.21	37	4.35
Further coronary thrombosis	59	4.15	31	4.28
* Active group	55	4.98	8	5.93
* Restricted group	133	4.59	52	4.54

* Includes only cases observed for at least one year.

cent.) died cardiac deaths: 11 from a second attack of coronary thrombosis, 3 from a third attack; 2 died 'suddenly' and 1 death occurred during a Stokes-Adams attack; 8 died of congestive heart failure.

Patients surviving attack by more than ten years. Table VI contains short summaries of the histories of eleven patients, 5.2 per cent. of the whole series, who are known to have survived the attack by more than ten years. It is interesting, in view of the statement of Gross (2) that the more extensive collateral circulation of older hearts renders them better prepared to withstand coronary occlusion, to note that almost half these survivors were more than 60 years of age before the attack occurred. All of them were in the hypertensive group; more than half had cardiac enlargement.

As already stated, the dividing line between the active and restricted groups is not sharp, and the term 'active' is used to indicate an *almost* normal life for the patient's age. Cases 3 and 5, both physicians, are interesting. The former although severely handicapped and classified as restricted, continued for years to carry on part of his practice. The latter, in whom angina of effort first appeared 43 years ago at the age of 25, continued to be fairly active in spite of a second attack of coronary thrombosis 13 years after the first, and of moderate angina on more than normal exertion; at the age of 68 he is still leading a fairly comfortable life.

The influence of hypertension on the prognosis. In the foregoing sections it will have been seen that hypertension, as such, does not adversely influence the prognosis following the attack. Table VII summarizes these findings. Furthermore, variations in the blood-pressure level from time to time were found to be without significance, and no prognostic value could be attached to a high pressure in the early months with a subsequent fall, or to the

TABLE VI

Eleven Patients Known to have Lived for More than Ten Years Following Coronary Thrombosis.

Case.	Sex.	Age at time of attack.	Hypertension.	Cardiac enl.	Activity.	Cause of restriction of activity.	Remarks.
1	M	53	+	+	R	Dyspnoea, I. C.	Living in 11th year
2	M	46	+	+	R	Angina pectoris, dyspnoea	Three subsequent attacks of coronary thrombosis. Living in 11th year
3	M	51	+	+	R	Angina pectoris, dyspnoea, I. C., paroxysmal tachycardia	P-R interval lengthened before attack. Now complete block. Living in 11th year
4	M	54	+	0	A	—	Died pneumonia in 14th year
5	M	46	+	0	A	—	Angina pectoris for 21 years prior to attack. 2nd attack in 13th year after 1st. Living in 22nd year
6	M	60	+	+	A	—	Living in 11th year
7	M	60	+	+	R	Dyspnoea, failure, bronchitis	Living in 13th year
8	M	64	+	+	R	Partial heart-block	Stokes-Adams attacks for 7 years; finally died in attack in 11th year
9	F	55	+	0	R	Angina pectoris	Three subsequent attacks of coronary thrombosis. Living in 17th year
10	F	63	+	not known	A	—	Living in 12th year
11	M	62	+	0	R	Angina pectoris, dyspnoea, I. C.	Living in 11th year

I. C. = Intermittent claudication. A = Active. R = restricted.

reverse, namely, a blood-pressure rising some time after the attack, even to a higher level than before it. Levine's (4) belief, that those in whom there was a pronounced fall with only slight subsequent rise fared better and lost any angina that they might formerly have had, could not be confirmed by my observations. Nor could any support be found for the suggestion put forward by Master (5) that efforts directed towards keeping the blood-pressure low tend to prevent further attacks of coronary thrombosis. The incidence of recurrent attacks was actually higher in the non-hypertensive than in the hypertensive group (see Table VII).

Indeed, the prognosis as to length of life appears to be rather better among those whose blood-pressure is high (Table V). This is in accord with the impressions of other authors (4), (10), (3), but no adequate explanation has been advanced. In the present series it was due partly to the fact that the non-hypertensive group contained the only cases of cardiac aneurysm, four in number; in three of these four that died the average duration of life was only 1.8 years. The chief factor may perhaps be the capacity of the coronary arterial system, which has been shown by Russow (9) to have a greater total lumen proportionally to the heart weight in hypertensives than in normal persons.

TABLE VII

Comparative Analysis of Hypertensive and Non-hypertensive Groups Surviving Coronary Thrombosis.

	Whole hypertensive group. (155 cases).		Non-hypertensive group. (57 cases).	
	No.	%	No.	%
Active life *	40	29.2	15	29.4
Restricted life *	97	70.8	36	70.6
Congestive failure	24	15.5	3	5.3
Dyspnoea (severe)	41	26.4	9	15.8
Angina pectoris †	91	58.7	32	56.1
Subsequent coronary thrombosis	42	27.1	17	29.8

* Only in patients followed for at least one year.

† Of all grades of severity, including that found in some patients in 'active' group.

Cardiac enlargement. The most important side of the hypertension problem in coronary thrombosis has to do with the influence exerted on the course of the disease by cardiac enlargement. Grant (1) has already shown the direct relationship of the latter to an unfavourable prognosis in another form of cardiopathy, namely, valvular disease.

Enlargement is due, in more than 80 per cent. of the coronary thrombosis patients in whom it is found, to hypertension, the effect of which seems to be exerted almost entirely before the attack (8). The reason why hypertension following the attack so seldom causes increase in the size of the already enlarged heart is probably to be found in the generally lower blood-pressure—the myocardium has previously adjusted itself to the increased load by undergoing hypertrophy, so that the new lower level, even though still hypertensive, is tolerated without difficulty. If it can be shown that the prognosis in patients with enlarged hearts is more unfavourable than in those with normal sized hearts, the indirect effect of hypertension, as opposed to its negligible effect per se, will have been established.

In Table VIII a comparison is made between cases showing enlargement and those with normal sized hearts. A decided superiority (almost double) in the percentage of active lives is evident in the latter group over the former (see also Table I). That hypertension per se was not a factor was shown on subdivision of the two groups into hypertensive and non-hypertensive; the corresponding percentages obtained from the 103 cases of enlargement with hypertension and from the 25 cases of enlargement without hypertension showed no essential difference from each other, and the same lack of difference was found on subdividing the group without enlargement (42 hypertensives and 30 non-hypertensives). These test tables are, in the interest of brevity, not presented.

It has already been recorded that congestive failure in the series occurred only in cases with enlarged hearts.

The symptom most closely associated with enlargement was dyspnoea on exertion; the size of the heart was increased in 90 per cent. of those in which shortness of breath was the sole cause of restriction. All the cases of

TABLE VIII

Comparative Analysis of Cases of Coronary Thrombosis With and Without Cardiac Enlargement.

	Enlargement. (128 cases).		No enlargement. (72 cases).	
	No.	%	No.	%
Active life *	27	23.1	25	39.1
Restricted life *	90	76.9	39	60.9
Congestive failure	24	18.7	0	0
Dyspnoea (severe)	44	34.4	5	6.9
Angina pectoris (all grades of severity)	78	60.9	42	59.7
Subsequent coronary thrombosis	39	30.5	16	22.2

* Only in patients followed for at least one year.

failure, except two with severe angina, had previously been restricted by dyspnoea. It is also undoubtedly true that angina of effort, by coming first into operation, often masked the shortness of breath which would otherwise have been the restricting factor.

While increase in cardiac size exerts through dyspnoea and failure a decided influence on the patient's activity, its unfavourable effect on the duration of life following the attack is not pronounced. Table V shows that those with large hearts are alive almost as long on the average as are those with normal sized hearts. The outlook as regards length of life in the dyspnoeic group has been described as particularly bad (3), but the findings in the present series have not corroborated this. Presumably the most serious are those that go on to gross congestive failure, yet in the 20 such cases that are known to have died, the average duration of life following the attack was only reduced by 10 per cent. (Table V).

Although the incidence of angina of effort subsequent to the attack bore no relation to the size of the heart, a higher than the average percentage of further attacks of coronary thrombosis occurred in the group with enlargement (Table VIII).

Summary

1. The prognosis, with special regard to the influence of hypertension and cardiac enlargement, has been studied in 212 cases of coronary thrombosis which survived the attack by three months.

2. More than one-fourth were able to lead fairly active lives. In the remainder angina of effort and dyspnoea on exertion (including chronic congestive failure) were the most important symptoms causing restriction of activity or invalidism, and these were operative in almost equal proportion. The active group lived longer following the attack than the restricted.

3. The onset and incidence of angina after coronary thrombosis were not related to the height, or changes in the height, of the blood-pressure, or to the size of the heart. Angina of every grade of severity, including that compatible with a fairly active life, occurred in 39 per cent. of cases prior to the attack and in 58 per cent. of cases following it; in less than 10 per cent.

did prior angina fail to recur after the attack. The presence of subsequent angina did not affect the average duration of life.

4. The incidence of dyspnoea severe enough to cause restriction of activity followed closely the incidence of cardiac enlargement. Hypertension was not more frequent in the dyspnoeic group than in the whole series.

5. Congestive failure, which affected 13 per cent. of the series, was found only in patients with enlarged hearts.

6. Subsequent attacks of coronary thrombosis occurred in 28 per cent., about half of them during the first two years. The incidence of these attacks was unrelated to the height of the blood-pressure, but was somewhat higher in cases with enlargement than in those with hearts of normal size. About one-fifth of these subsequent attacks were fatal.

7. The duration of life following the attack averaged 4.2 years in 65 cases known to have died. Hypertensives appeared to have a somewhat more favourable outlook in this regard than non-hypertensives. The groups with cardiac enlargement and with congestive failure showed a slight reduction in the duration of life, which was, however, unaffected in the average by further attacks of coronary thrombosis.

8. A statistical table is presented showing the rate of survival based on experience of the series.

9. Short summaries are given of the histories of eleven patients (5 per cent. of the series) known to have lived for more than ten years following the attack.

10. Blood-pressure changes and the height of the blood-pressure following recovery from an attack of coronary thrombosis are on the whole of little significance.

11. Cardiac enlargement is a most important factor in causing restriction of activity; the expression of its influence is dyspnoea on exertion, and in the most severe cases congestive failure.

12. The probability that following recovery from an attack of coronary thrombosis a patient will be able to lead a fairly active life is almost twice as great in those with normal sized hearts as in those with cardiac enlargement.

I am deeply indebted to Dr. John Parkinson for placing his case-notes at my disposal and for his helpful advice in the preparation of this paper.

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THE HEART IN EMPHYSEMA¹

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With Plates 1 to 3

CERTAIN chronic diseases of the lung may produce a secondary effect upon the heart with the production of what has been variously termed pulmonary heart disease, cor pulmonum, or emphysema heart. Such a division is in keeping with the current tendency to divide heart disease according to its etiology, e.g. congenital, rheumatic, hypertensive, arterio-sclerotic. So also a pulmonary form has come to be distinguished, and with good reason, for it has importance as a direct cause of cardiac enlargement and of congestive heart failure.

There are particular difficulties in the recognition of this type of heart disease. One of them is that an entirely different source of cardiac disease or failure is often found combined with it, namely hypertension. Apart from this, and dealing with those affected by chronic lung disease alone, difficulties still remain. One fundamental source of these is the similarity of cardiac and pulmonary symptoms, and another the scantiness of physical signs implicating the heart. Symptoms arising from the pulmonary lesion resemble too closely those of cardiac disease to form an easy means of distinction; they are of the same order with dyspnoea dominant. The pulse remains regular and the rate need not be much increased. The cardiac impulse may owe its position to displacement rather than to enlargement of the heart, or else it is impalpable. Percussion has its peculiar fallacies, and in any case is invalidated by emphysema. Again, of the signs relied upon to disclose congestive failure, oedema alone, perhaps coupled with an enlarging liver, retains its usual significance. Distension of veins in the neck is often seen in emphysema without cardiac failure, and crepitations at the bases and elsewhere may arise from capillary bronchitis or broncho-pneumonia.

All this shows the difficulty, or even impossibility, of demonstrating with current clinical methods any consecutive involvement of the heart in chronic lung disease. A new method of approach is demanded; and if oedema is the test of cardiac failure in such a case, enlargement of the heart is the test of cardiac involvement in the absence of failure. As radiology is the clinical method of choice, we have attempted by this means to study the question of cardiac enlargement in emphysema. This particular disease has been selected because it is common, and because cardiac enlargement in its course is notoriously difficult to recognize by other methods. In other chronic lung

¹ Received October 12, 1936.

diseases where fibrosis predominates, displacement of the heart and distortion of its outline render judgement of heart-size difficult, even by the radiological method. The literature dealing with cardiac enlargement will first be discussed briefly from the standpoint of morbid anatomy and then more fully in relation to radiology. Our own investigations on a series of 80 patients will then follow.

The Literature on the Morbid Anatomy of the Heart in Emphysema.

Until some twenty years ago, knowledge of heart-size in emphysema rested almost exclusively upon reports of necropsies. For more than a hundred years these appeared sporadically in the literature, and it became the general opinion that enlargement of the right side of the heart was a frequent result.

Senac (70) in 1783 wrote of cardiac enlargement in asthmatics as observed by himself and by previous writers. He cited especially enlargement of the right auricle and dilatation of the pulmonary artery as within his own experience. About fifty years later Louis (56) remarked that enlargement of the heart was found in all cases dying from emphysema which had oedema; he found it in 16 of 42 cases seen at necropsy. A few years later Budd (10) described the remarkable reduction in the capillary circulation in the lungs, leading to obstruction to the circulation through the pulmonary arteries, and hence to dilatation of the right side of the heart, and later to the oedema 'so frequently met in emphysematous persons'. Laennec (50) mentioned both hypertrophy and dilatation of the heart and dilatation of the pulmonary artery as a sequel to emphysema; he described four cases, in one of which the heart was normal, and in the other three enlarged, including the left ventricle in all. Chevers (13) wrote 'It is usual to find the pulmonary artery with its valves more or less (sometimes extremely) dilated, coarse in structure and irregularly thickened and opaque, in cases of old bronchitis and emphysema of the lungs'. He thought that the entire tract of the pulmonary artery was usually affected in this way, with the branches varicose and atheromatous, and sometimes in extreme examples with marked thickening of the main trunk and pulmonary valves. In the same year Sibson (71) described and pictured the post-mortem appearances in a patient who died from extreme emphysema with congestive heart failure; the heart weighed $14\frac{1}{2}$ oz. and there was excessive enlargement of the right side, including the conus pulmonalis and the pulmonary artery. The right ventricle almost completely concealed the left. Gairdner (26) discounted the view that obstruction to the pulmonary circulation led to the enlargement, as the left side of the heart was so often involved. He said that he had never seen marked enlargement of the right side without involvement of the left at the same time: this, however, was at a time when hypertension was not recognized if without chronic renal disease. Peacock (63), van der Byl (11), and Waters (79) described series of cases in

relation to enlargement, and all noted its frequency and bilateral nature. Within the next few years Johnson (40), Jenner (39), and Greenhow (28) again emphasized these points.

From this time onward opinion remained constant that the consecutive changes in the right side of the heart were dependent upon vascular obstruction in the lungs. But although it received some reference in the literature in a general way, only a few writers have added further facts. Hamilton (33), in his fine book, gave a summary of the morbid changes in the heart in his own series of cases. Hirsch (34), and some years later Winderöe (81), did the same though more briefly. Bret (9) also detailed a small series of necropsies; in comments upon the clinical features he noted especially the rarity of auricular fibrillation as contributory to enlargement, contrasting this with its frequency in mitral stenosis and hypertension. This was the first mention of this important point. Kirsch (42, 43), in the course of his studies on the development of cardiac enlargement, reported six examples of emphysema. By exact weighing of the separate chambers, and also by linear measurements, he showed that, taking a single ventricle, the process of dilatation (and hypertrophy) always began in a particular portion of it (the 'outflow tract'), and only later was the rest of the ventricle implicated (the 'inflow tract'). The outflow tract of the right ventricle extends from the apex to the pulmonary orifice, involving thus the anterior wall, and every enlargement of the chamber begins here as a lengthening which is betrayed by prominence of the conus, i.e. the far end of the outflow tract. When the inflow tract is affected, and it is never affected until later when the outflow tract has acquired its characteristic change, it is a widening or broadening of the inflow portion of the ventricle which occurs. These anatomical studies upon the way in which enlargement develops have been confirmed for emphysema, as we shall show by our radiological results. Recently Brenner (8) has cited hypertrophy of the right ventricle in 12 out of 26 cases of emphysema.

Isaaksohn's (36) account in 1871 of the detailed histological changes in the lungs has scarcely since been amplified in any important respect; the widespread narrowing and later thrombosis, rupture, and atrophy of capillaries which he described has formed the anatomical basis upon which has been founded subsequent opinion upon cardiac involvement by the disease. Later injection experiments upon cadavers have demonstrated a reduction of the vascular bed in certain cases. Yet a few writers have questioned the importance of these changes as a cause of cardiac enlargements (20, 35, 52). White and Brenner (80) have also remarked upon the rarity of the 'cor pulmonale'; they contend that it is not ordinarily produced even by high degrees of emphysema or other chronic lung disease.

Another factor, sclerosis of the pulmonary vessels, has also to be computed. Arillaga (3), Savini (68), Warthin (78), Eppinger and Wagner (24), Miller (59), Clarke, Coombs, Hadfield, and Todd (15), and others have written of its connexion with chronic lung disease, including emphysema. There can be

no doubt that a sclerosis of the smaller pulmonary arteries can provoke enlargement of the right heart. But the recorded cases of its proven association with emphysema are so rare that it cannot so far be given an important place as a contributory factor in this disease. There are a few examples among the references just quoted; and Lutembacher (57), Ribierre and Giroux (65), Jagić and Spengler (38), and Rosenthal (66) have recorded others where chronic bronchitis and emphysema terminated in congestive failure, and where the pulmonary arterioles were thickened and obliterated. All these cases closely resembled those of Arillaga. With these exceptions, none of the accounts of the histology of the lungs in emphysema make any mention of concomitant endarteritis (36, 37, 33, 5, 53, 58, 54, 74, 41, 61).

A further problem that has already been raised is to account for the enlargement of the left side of the heart constantly referred to by the earlier writers. Gee (27) suggested the explanation when he spoke of chronic bronchitis as seldom unassociated with either chronic nephritis, chronic myocarditis, or atheroma. Gull and Sutton (30) found granular kidneys in 22 out of 33 cases of emphysema. Such associated lesions have often been referred to since as contributory to the cardiac enlargement and failure in emphysema (14, 38, 55), but investigations to show the exact significance for the heart of associated cardiovascular lesions in emphysema have been few. Chabert (49), in a series of 258 cases, found myocardial disease alone in 30, myocardial and valvular disease in 58, myocardial disease and aortic atheroma in 15, valvular disease alone in 18, and aortic atheroma alone in 19. Curschmann (18) found a systolic blood-pressure of 150 mm. Hg or more in 19 out of 48 cases; though only once in 15 cases with serious congestive heart failure was hypertension thought to be an important additional factor. On the other hand, Kountz, Alexander, and Dowell (46) did not find any histological evidence of myocardial disease in nine cases studied at autopsy, and in one only was there enlargement. Yet in a subsequent paper Kountz, Alexander, and Prinzmetal (47) described dilatation of the right ventricle in as many as 10 out of 17 cases at necropsy, with hypertrophy of both right and left ventricles in most of these. They consider that the cause of the left ventricular hypertrophy is unknown, and hypertension is not cited as a cause in their series. From our experience we would think it likely that a proportion of their cases had at some time, even before they came under observation, been subjects of hypertension. Indeed, it would be remarkable if it had been wanting in at least a proportion of ten patients dying with non-valvular cardiac enlargement.

The Literature on the Radiology of the Heart in Emphysema

Dietlen (21) was perhaps the first to study the heart in emphysema by X-rays. He compared the orthodiagram found in the emphysematous with that of patients with mitral and other valvular disease. He thought that the characteristic form approximated to the 'cœur à goutte' of French

authors, in that it looked small, was placed vertically and almost mesially, and especially that it extended low—almost into the abdomen—owing to the low diaphragm. The only further stage, and the anterior view only is here considered by him, is a modification of this drop-like heart by the assumption of a rounded corner on each side adjoining the diaphragm, so that the whole orthodiagram is somewhat triangular. Incidentally Dietlen also reproduced two orthodiagrams showing the apparent reduction in size which takes place during an attack of asthma, where, however, the diaphragm descends still lower. Groedel (29) in 1912 gave a general account of the radiology of the heart in emphysema. He remarked its apparent smallness and hanging appearance, as in enteroptosis, and in advanced cases its enlargement transversely. The 'dropped heart' with its median position and narrow appearance has since had passing comment as a feature in emphysema by Staehelin (73), Dietlen again (22), and Assmann (4); there is general agreement that a low position of the diaphragm is the chief factor. For the same reason the aortic knuckle may also have a lower position than normally.

Staehelin (73) thought that there was often cardiac hypertrophy, but that it might easily be overlooked. He knew that this enlargement had similarities to that met in mitral stenosis. In 1916 Lutembacher (57), in an important paper, described both the radiological and pathological appearances in five cases with tricuspid incompetence and heart failure. Here the heart assumed a sabot shape due to great enlargement of the right ventricle, which occupied the entire anterior surface. Often there was also great prominence of the pulmonary arc. Rouslacroix and Perrimond (67) have since described a similar case in which there was an organized thrombus in the right pulmonary artery. Dietlen (22), in his book, described briefly the considerable enlargement of the right heart which may occur. He showed that as the left heart might be small there was not necessarily an increase in the total size of the heart's shadow. If the left heart was enlarged as well as the right, the combined changes gave a 'cornered' or triangular appearance to the outline. More recently Uhlenbruck (76), dealing with cardiac failure in chronic lung disease, remarked upon the right ventricular enlargement as seen especially in the left (II) oblique position, though it might be absent radiologically even when demonstrable at necropsy.

Alexander, Luten, and Kountz (2) found little evidence of cardiac involvement in a series of 50 patients with long-standing asthma and emphysema. Orthodiagraphic measurements of heart size were normal in 37, small in six, and large in six, though two of these had hypertension. In a later paper, Kountz, Alexander, and Dowell (46) noted enlargement of the heart in eight only of 66 cases of advanced emphysema, and in all these the enlargement was general; in two hypertension was associated and in two others syphilis, though without aortic incompetence. Podkaminsky (64) doubted whether enlargement was frequent or whether right ventricular enlargement formed the distinctive feature of the emphysema heart on

radiography. Crieep (17) found a slight increase in the transverse diameter in four out of 50 cases of asthma as the only evidence of enlargement.

Vaquez and Bordet (77) also noted the frequency with which the heart appeared to be normal, even in the most chronic cases. When enlargement occurred, its effect upon the right ventricle led to an increase in the transverse diameter ('transverse type'), or else the heart assumed the shape of a wooden shoe ('sabot'). In this event, though the lower left ventricular margin was spherical yet this was not from true enlargement of this chamber, but a result of its displacement to the left and upwards by the enlarged right ventricle. Assmann (4) gave as the early signs an increased curvature of the lower part of the right border with prominence of the pulmonary arc and conus pulmonalis. He mentioned the increased hilar shadows, but did not consider that pulmonary arteriosclerosis was contributory. Clerc and Mourrut (16) have detailed the radiological changes at the hilum in one case of long-standing emphysema due to chronic bronchitis; along with an enlarged pulmonary arc the hilar shadows were excessively pulsatile and formed a 'moustache' of tortuous vessels hanging downwards on the right and left. The shadows of the main pulmonary arteries formed very abundant arborizations spreading into the lungs, and in the left oblique position the main pulmonary artery and its left branch appeared to be lengthened, widened, and of increased density. The writers thought that these radiological appearances implied coexistent pulmonary arteriosclerosis, though Laubry, in a discussion, doubted whether they might not result simply from enlargement of the pulmonary vessels. In a recent paper Udvardy (75) referred both to the small heart and to the enlargement of emphysema. The latter involved the right side chiefly, but in contrast with left-sided enlargements was much more difficult to discern. Enlargement of the pulmonary artery and its large branches might be so great as to simulate that found with congenital heart disease or mitral stenosis. However extreme the involvement, in emphysema the left auricle escaped. No single configuration of the heart's shadow, however, was considered as characteristic of the emphysema heart. Binhold (7), recently reporting on a series of cases, found a slight increase in the radiological heart volume as measured by Kahlstorf's method.

Choice of Cases ; Clinical Features

Our investigations were made on a series of 80 patients with hypertrophic emphysema. Most of these were gradually assembled at the Cardiac Department of the London Hospital over a period of three years, and a number gleaned from other hospitals and from consulting practice were added. These provided further opportunities of study though weighting the proportion of emphysema patients showing cardiac lesions.

Certain criteria were selected for the clinical diagnosis of emphysema.

There are difficulties which have been voiced by Cabot (12) arising from discrepancies between clinical diagnosis and post-mortem findings. He looks upon the barrel chest as a manifestation as important as the lung signs in recognizing this condition. It is still the general opinion, however, that the pulmonary changes are the essential feature in these patients, and that as a disease it is fairly common and characteristic. We would agree, however, that the diagnosis must always rest upon a systematic conjunction of abnormal signs. The incidence of the most important of these in our series is given in Table I.

TABLE I

*Analysis of 80 Patients with Emphysema**Evidence of Emphysema*

(1) <i>Clinical</i>	
Heart sounds distant	79 cases
Cardiac and hepatic dullness reduced or obliterated	74 "
Raised, rigid, barrel chest	69 "
Hyper-resonance	68 "
Prolonged expiration	67 "
(2) <i>Radiological</i>	
Excessive translucency of lung fields	36 cases
Wide intercostal spaces	53 "
Low flat diaphragm	59 "
Defective diaphragmatic movements	43 "
Arched sternum	42 "
Flaring of lower ribs	42 "
Kyphosis	41 "

In 67 out of the 80 cases every important clinical characteristic was present; in the remaining 13 some of the signs were absent, though a minimum of three at least were present in each patient. This standard thus excluded from the series many patients with chronic bronchitis in whom the presence of emphysema, though probable, was not certain. It might be thought that radiological evidence would have furnished sufficient proof in some of these, but of this we remained unconvinced. Even in those included in the series where the clinical evidence of emphysema was ample, radiology gave additional support to the diagnosis only in about half. In individuals this support was striking, but the statistical figures were less valuable than was at first anticipated (Table I).

Clinical features. In the series of 80 cases, 66 were males and 14 females. Only adults were included, and their ages ranged from 34 to over 70 years; four were under 40 and three over 70 years of age. In 78 the emphysema was based upon chronic bronchitis, with asthma in addition in 29.

The duration of symptoms was less than a year in two, from one to five years in 13, from six to ten years in 14, from eleven to twenty years in 22, and over twenty years in 23; in six the duration was uncertain. Thus in 59 of the 80 cases the duration was over five years, and in many of these had led to disablement from work. Dyspnoea on exertion, and cough with sputum were constant features. The copious foetid sputum of infected

bronchiectasis was always absent, but in a few where gross bronchial dilatation was suspected lipiodal bronchography was negative. A history of haemoptysis was obtained in 20, and of pain in the chest in 31 (pleuritic in 11, anginal in three). Fifty complained of weakness, but other evidence of constitutional disturbance was exceptional. Tachypnoea at rest was noted in 53, cyanosis (usually slight) in 46, and clubbing of the fingers in 19. Sixty-four patients had bronchitis at the time of examination, and in 22 of these there was associated bronchial spasm.

Ten showed radiological evidence of localized obsolete tuberculous lesions and two had thoracic deformity with kyphoscoliosis. No tubercle bacilli were found in the routine examination of the sputum. The Wassermann reaction was negative in 27 in whom it seemed desirable to have it tested. A full clinical examination of the cardiovascular system was made in each patient and an electrocardiogram was taken. The results will later be correlated with the special radiological investigations.

Radiological Methods and Criteria of Enlargement

All patients were first of all screened in the anterior, both oblique, and complete lateral positions. In addition, six-foot teleradiograms were taken in the anterior position with the patient standing at the end of a deep inspiration; in the majority they were also taken in both oblique positions.

The diagnosis of enlargement was never based on screen examination alone, though often this revealed changes later confirmed from the films. Simple inspection of these will often show at once whether the heart is enlarged or not, and experience in the interpretation of such films, normal and pathological, cannot fail to facilitate the detection of departures from the normal.

Sometimes, however, the presence or absence of enlargement will be open to doubt if inspection only is used, so that cardiac measurements, to be compared with published tables of normals, would be expected to help. In such tables, heart size is correlated with body-weight, as the ratio of heart-weight to body-weight has been shown by anatomical observations to be fairly constant (72). From the anterior silhouette the total transverse diameter and the oblique (or long) diameter can be obtained, and of these two the first is both more often measurable and more useful as an indication of heart size.

The fact that our teleradiograms were taken at the end of deep inspiration prevents us from using them for measurements which can be compared with normal tables which have been compiled from orthodiagrams or from teleradiograms taken in mid inspiration. Notwithstanding this serious objection an attempt was made to measure (1) the transverse diameter, (2) the cardio-thoracic ratio, and (3) Fray's method in oblique positions. In our series the transverse measurements were compared with those given by Hamer (32), Vaquez and Bordet (77), and Schinz and others citing Dietlen

(69). Such measurements, though open to many objections if applied in doubtful cases of enlargement, do at least provide measurement for great enlargements, and serve as a comparative standard in the same individual.

In our series the transverse diameter of the heart was measured in 50 cases. In 22 of these it was greater than the average normal figure from a composite table given by Edens (23), and in seven greater than the maximum normal figure. Of the total of 22 cases with excessive transverse diameter, enlargement as judged by inspection of films was present in 16, involving the right heart in four, the left in four, and both in eight. Four others had doubtful slight enlargement of the right side judged in this way, so that in two only did the measurement point to enlargement missed by simple inspection. Of the remaining 28 cases in which the transverse diameter was normal, three had enlargement of the right side, four enlargement of the left side, while 15 had no enlargement and six were doubtful. Thus in the entire series the transverse diameter suggested an enlargement in two which was not confirmed in other ways, and in seven failed to confirm it when inspection of films pointed to it quite definitely. In our opinion the measurement is much inferior in value to simple inspection of films as a means of deciding the presence of enlargement.

In the normal chest the total transverse diameter of the heart bears a fairly close relation to the maximum (internal) transverse diameter of the chest though not in patients who are overweight. This ratio, internal chest diameter/horizontal heart diameter, has been determined in normals either from orthodiagrams (31, 19), or from teleradiograms taken after a moderate inspiration, as a deep inspiration upsets the ratio even in health. As our films were taken always in full inspiration in order to obtain the clearest cardiac outline, measurements from them are not strictly comparable with the published normal figures, but we used the comparison in selected cases with this reservation.

Variations in the normal heart-lung ratio depend mainly on the shape of the chest and the position of the diaphragm. At once doubt will therefore arise in applying the ratio as a measure of enlargement in emphysema. The broad chest tends to raise the cardio-thoracic ratio, whilst the low position of the diaphragm, producing a vertical lie of the heart, tends to do the same. Estimation of enlargement in emphysematous subjects will, therefore, be conservative, and considerable enlargement may, in fact, occur before the ratio falls below the normal limit. Our figures confirmed this view. The ratio was determined in 50 cases in the series where exceptional variations in bodily habitus were absent. In all, excepting seven, the ratio was within normal limits. Yet of the 43 with a normal figure, 15 had other radiological evidence pointing to localized enlargement, which affected the left heart in seven, the right heart in five, and both in three. The same short-comings of this criterion apply also to mitral stenosis when the only visible enlargement from in front is at the conus of the right ventricle.

In all seven with an abnormal ratio (below 2.00) we had felt no doubt of

the enlargement after simple inspection of the films. Four had hypertension, with bundle branch-block in one, intraventricular block in one, and auricular fibrillation in another as contributory factors. The remaining three also had evidence of myocardial disease as shown by intraventricular block in one, abnormality of QRS complexes in Lead II in another, and negative T-waves in Leads II and III in another. Thus every one of the seven cases with an abnormal cardio-thoracic ratio had a contributory cause for the enlargement which the ratio confirmed. None of the 50 cases studied in this way had an abnormal ratio that could be attributed to the effects of the lung disease alone.

There would be advantages in a reliable scheme for measuring enlargement of individual chambers of the heart and of the great vessels. But we are convinced that this is not yet feasible except when such enlargement is of a very gross kind. The difficulties are twofold: in the first place it is often impossible to secure, either on screening or from films, reliable points from which to take the required measurements; and secondly, the data (even if obtainable) may be falsified by an abnormal development of neighbouring contours. For these reasons we have rejected for routine purposes such standards of measurement as those applied by Vaquez and Bordet (77) and Abreu (1) to the pulmonary arc. They have no exact anatomical counterpart, and often mislead. We believe that the general opinion of a trained observer based upon a screening examination and inspection of teleradiograms is a more reliable guide to the presence or absence of enlargement. An extension of this scheme of measurement in the left (II) oblique position has been put forward by Fray (25). He claimed that in normals and in a variety of cardiovascular conditions the position of the interventricular septum may be determined, and from this a measure of either left or right ventricular enlargement may be obtained. In addition, the transverse diameter of the heart may be compared with a transverse diameter of the chest in this oblique position to give a new cardio-thoracic ratio. In no cardiac lesion more than that due to emphysema would such a bilateral measure be of greater value, and we, therefore, applied Fray's measurements to our series. Fray himself drew attention to their inaccuracy with spinal or thoracic cage deformities, and we soon found that in emphysema the associated kyphosis and forward projection of the ribs and sternum, led to serious errors from the increased depth of the thorax and altered position of the heart. Both factors operate in the same direction with his system of measurement to place the interventricular septum too near to the margin of the left ventricle. Measurements of the size of the left ventricle will thus be below their true value; those of the right ventricle will be excessive. These objections were fully substantiated by measurements on typical radiograms exactly following Fray's rules. The interventricular septum appeared in impossible positions, often quite close to the left ventricular margin. We were compelled to conclude that the method was completely invalidated by emphysema.

Clinical cardiovascular features. These are summarized in Tables II and III. Simple clinical evidence that the heart was involved by the lung affection was usually wanting. For instance, persistent tachycardia was present in 36 only, and was slight (under 100) except in nine of these. Normal rhythm was the rule, and had been retained in all but one who had auricular fibrillation, with hypertension, as an addition. Accentuation of the second

TABLE II
Analysis of 80 Patients with Emphysema

<i>Clinical Cardiovascular Features</i>	
<i>Tachycardia</i>	
Under 100	28 cases
Over 100	9 "
(Normal rhythm in 79 cases, i.e. in all but one)	
<i>Associated cardiovascular disease</i>	
Hypertension (over 200 mm. Hg, systolic in 8; 5 with heart-block; 1 with abnormal QRS complexes; 1 with inverted T-waves in Leads II and III; 1 with auricular fibrillation)	28 "
Arteriosclerosis	20 "
(1 with abnormal QRS complexes; 1 with T ₂ and T ₃ inversion)	
Abnormal QRS or T-waves only	3 "
(Congestive heart failure	13 "
Contributory hypertension	5 "
Contributory hypertension and myocardial disease (EC)	2 "
Contributory myocardial disease (EC)	2 ")

sound at the pulmonary area was present in three only; and a pulmonary diastolic murmur was never heard. The supervention of congestive heart failure was seen in 13 cases only throughout the period of observation (two to three years), although it was anticipated and sought for with the greatest care. As many of the patients had had chest symptoms for many years, it is thus evident that emphysema alone seldom leads to congestive heart failure, and then only late in the disease.

It might be thought that failing clinical evidence, the electrocardiograph might point to a cardiac involvement in emphysema. If so, this would be in the form of right-sided preponderance, or perhaps as evidence of auricular hypertrophy in tall, broad, or bifid P-waves, or small voltage curves, particularly in Lead I. M. Winternitz (personal communication) thinks that a small P in Lead I with a high and pointed P in Leads II and III is significant of the emphysema heart, and that a bifid P is in contrast found in mitral stenosis. Certainly we have not seen a bifid P of note in emphysema, though we found only four examples of the P modification which he has connected with emphysema. In our series, electrocardiographic evidence proved to be of little help. Right-sided preponderance was present in 12 only, and was slight in eight of these. Changes in the P-waves were found in seven; in six they were unduly tall, twice in Lead II, and four times in Leads II and III; and in one they were unduly broad in Leads II and III. A small voltage curve in Lead I only was present in 14 cases, and in all

leads in five others. There was thus electrocardiographic evidence of one kind or another pointing to enlargement on the right side of the heart in 23 cases only out of 60 in whom records were taken. In 13 of these such evidence was quite striking in that two at least of the changes were present in each case, and the records approximated to those of mitral stenosis closely. Statistically, however, the electrocardiogram was an uncertain guide to involvement of the right heart. Six of the 23 in whom there seemed to be evidence of right heart enlargement had a normal cardiac size and outline radiologically. In two of these, indeed, the heart appeared to be small. On the other hand there were 11 other cases, with isolated enlargement of the right heart radiologically, where supporting electrocardiographic evidence was completely absent.

Although the heart so often escapes directly the effect of emphysema, it was often found to be involved to an important degree by independent cardiovascular disease. Hypertension was the most frequent association; the blood-pressure was raised (over 160 mm. Hg systolic) in 28 of the 80 cases. All these, with one exception, had dominant pulmonary symptoms, so that the hypertension was unsuspected until the sphygmomanometer was used. Arteriosclerosis, as shown by thick and tortuous radial and brachial arteries, often with visible deformity of the aorta on X-ray examination, was present in 20 cases. Five of these also had hypertension. A degree of heart-block was present in seven, five of whom also had hypertension; one had a prolonged P-R interval, three bundle branch-block, and three intra-ventricular block. Deformity of the QRS complexes in at least two leads was present in five others, and flat or inverted T-waves in three—all evidence of myocardial disease, most likely the result of coronary sclerosis.

In the entire series of 80 patients, therefore, 48 had independent and unobtrusive cardiovascular disease. This high incidence emphasizes in an unexpected way the part that the heart may play clinically in emphysema, quite apart from any direct involvement by the lung disease. This point is further stressed by those patients who had heart failure. The series of 13 cases with failure out of the total of 80 is a small one, but the only two essential clinical factors in the supervention of failure, were prolonged duration of the chest symptoms and the presence of hypertension (Table II). Hypertensive heart disease was found in 21 out of 67 without heart failure, and in seven out of 13 with heart failure.

Not only does hypertension contribute greatly to the production of failure in emphysema, but it also affects the prognosis when failure supervenes. In our series of 13 cases with failure, five died during observation. Three of these were examples of pure chronic lung disease, one had hypertension also, and another bundle branch-block. All of them died within a year of the first signs of failure, three within three months, and the other two from recurrent failure five and six months after improvement from a first attack. Congestive failure purely from chronic bronchitis and emphysema is rare and it is of grave prognosis. We have not seen, nor does the literature seem

to contain, instances of such patients who survived and had recurrent failure in any way comparable with rheumatic heart disease or hypertension.

Radiological Results

A summary of the chief radiological features appertaining to the heart and great vessels in each patient is given in Table III. The particular changes will first be described, and later will be discussed together in reviewing their comparative importance.

The pulmonary artery and its branches. Normally in an anterior radiogram only the left border of the main pulmonary artery is to be seen where it forms a part of the left border of the cardiac shadow, as the pulmonary or middle arc immediately below the aortic knuckle. In the normal heart this arc is concave, flat, or slightly convex; it is relatively prominent in young persons and in right dorsal scoliosis, and with adjacent pulmonary fibrosis.

In normal anterior radiograms the hilar shadowing of the lungs is mostly composed on each side of the cardiovascular shadow, by the two main branches of the pulmonary artery and their subsidiary divisions (Plate 1, Fig. 1). The *left* one runs transversely outwards from the pulmonary arc for about one or two centimetres and then curves sharply to run downwards and slightly outwards and then slightly inwards towards the base of the lung; the lower part is lost behind the cardiac shadow. In its mid-portion, just after turning to run downwards into the lower lobe, the vessel is crossed by the left bronchus so that its outline is here often lost for a short distance. Sometimes in normals, and especially if the heart is displaced to the left or if the pulmonary arc or conus are enlarged, the inner border of the left pulmonary artery is overlapped and obscured. Only the outer part of the vessel can then be seen as it descends, and this may lead to confusion in that the shadow of the vessel may so blend with those of the main pulmonary artery and conus as to suggest that they are enlarged more than they are in reality.

The *right* pulmonary artery is better seen than the left in anterior radiograms because it is free of the cardiac shadow. It emerges into view from the right border of the pedicle just above the junction of this with the right auricle and at or just below the level of the pulmonary arc on the left. Thence it runs directly outwards for a centimetre or so and then sweeps downwards and slightly outwards at first and then downwards and slightly inwards towards the base of the lung.

In oblique and lateral views the pulmonary artery and its two main branches are in some respects to be seen even better. In the left (II) oblique position (Plate 1, Fig. 2) the origin and outline of the pulmonary artery is obscured as it is overlapped from above by the ascending aorta and superior vena cava; much of the vessel lies in the same plane, so that a single dense supracardiac shadow is seen that includes both vessels. From this shadow the pulmonary artery curves backwards and slightly upwards to its bifurcation below the aortic arch, though this can scarcely be distinguished. Here under

favourable conditions, and especially in elderly or emaciated subjects, the vessel may be seen as a rounded shadow of considerable density forming the anterior limit of the 'aortic window'. This increased density would seem to be due to the fact that the direction of the rays in left oblique positions greater than 30° approximately follows the course of the receding right pulmonary artery. The actual bifurcation of the main vessel thus comes to acquire a fictitious density from the superimposed shadow of the right branch seen in longitudinal profile.

The normal left pulmonary artery can often be seen leaving the bifurcation to run backwards across the middle of the 'aortic window' towards the spine (Plate 1, Fig. 2). It has a slightly curved course with an upward convexity for about three to four centimetres and then turns sharply downwards. At about this point it is crossed by the left bronchus and thereafter is often lost to view in normals. In its course it constitutes a secondary or lesser arch, a pulmonary arch below the aortic arch.

In the right oblique position (Plate 1, Fig. 3) the anterior edge of the pulmonary artery forms a small part of the upper portion of the anterior cardiac outline. It passes backwards and is recognized as a rounded dense area as it is seen dividing. Below, the artery joins the conus pulmonalis. How much of this conjoint shadow is normally composed of pulmonary artery and how much of conus is not yet decided, but Koch and Wieck (44) figure the pulmonary artery and not the conus as forming this border exclusively in both their figures, one a senile and the other a drop-like normal heart. Laubry and his collaborators (51) show similar figures in their recent work.

We found radiological changes in the stem and branches of the pulmonary artery to be the most frequent in emphysema—far commoner than enlargement of the heart itself. One of the most striking and most frequent changes was the excessive root shadows seen in anterior films (Plate 1, Fig. 4). The vascular markings of the hila appeared to us beyond the normal in 37 out of the 80 cases. In seven this change was great, and in 30 moderate. The right and left branches of the pulmonary artery were enlarged and often denser than normal; also they extended farther into the lung fields. The whole appearance was one of increased hilar and perihilar vascularity, with the large main branches of the pulmonary artery often hanging downwards on each side like a drooping moustache.

In addition to the fuller branches, prominence of the pulmonary arc from enlargement (Plate 1, Fig. 4) was found in anterior radiograms in 22, in 13 moderate in degree, and in nine slight. Usually an increase in the convexity of the arc accompanied the undue prominence. Even where the arc appeared enlarged abnormal pulsation was not specially noticeable on screen examination. The great enlargement of the pulmonary arc often seen in mitral stenosis or congenital heart disease was never met, nor was the excessive pulsation described in pulmonary sclerosis or patent auricular septum.

An enlarged and projecting vascular arc was not, we believed, the only radiological evidence of enlargement of the main stem of the pulmonary

artery to be seen in the anterior position. An important source of difficulty in gauging the size of the pulmonary arc in emphysema was that the abnormal development of the left branch sometimes obscured the usual sharp outline of the stem. Not only so, but *the arc, as such, might not exist at all*, the main vessel merging imperceptibly into the left branch without presenting any edge which could be seen or measured as an arc (Plate 2, Fig. 5). The disappearance of the arc then became the criterion of enlargement of the main vessel. This feature was found in 25 cases in our series, very clearly in 10. These, together with the other 22 in whom an abnormally prominent arc was present, make up a total of 47 cases in which enlargement of the main pulmonary artery was present.

These changes in the pulmonary artery and its branches led to characteristic appearances when viewed in the oblique positions. Here the dividing pulmonary artery was often (38 in 80 cases) to be seen in films as an unusually dense well-demarcated rounded or oval shadow, particularly in the left (II) oblique position. Another frequent abnormality was seen in the left oblique position, namely, undue prominence and density of the left pulmonary artery (37 in 80 cases) (Plate 2, Fig. 6, also Plate 3, Fig. 11). The vessel could be seen arising from the dense shadow of the bifurcation as a clearly defined shadow extending backwards across the aortic window and then downwards towards the base of the lung. It was larger, and was seen more clearly and farther than in normals. Sometimes its descending branch was easily traced as far as the diaphragm. In the right (I) oblique position, though the greater density of the dividing pulmonary artery was often to be seen, the right branch could only occasionally be defined as a separate structure.

In the left (II) oblique, and also in the right (I) oblique position, there is even a superficial resemblance to the *unfolding of the aorta* which is seen in aortic sclerosis with or without hypertension. There are, of course, fundamental differences, chiefly that in pulmonary hypertension such as that with which we are dealing the conus and pulmonary stem and right or left pulmonary artery respectively—which combined give the unfolded appearance—are all themselves dilated. Yet the dilatation of the aorta in syphilitic aortitis does not prevent an element of unfolding of the aorta from appearing in this lesion as Kudisch has shown (48).

The impression on the oesophagus made by the pulmonary artery (with the left bronchus), in particular the beginning of the right branch, as shown radiologically with barium in the oesophagus, was not found to be of much additional value as a guide to the moderate enlargement of the vessel met with in emphysema, though it can be demonstrated (Plate 2, Fig. 7). Occasionally a combined aortic and pulmonary artery curve, beyond that which can occur normally, was present.

The conus of the right ventricle. Enlargement of the conus was the most frequent indication of actual cardiac enlargement in emphysema, though it was found less often than the changes in the branches of the pulmonary artery or its main stem already described.

In our series enlargement of the conus was present in 33 of the 80 cases. In nine the enlargement was slight, and in 24 moderate; extreme enlargement was not seen. The degree of enlargement was, on an average, much less than in mitral stenosis. It was rarely demonstrable in the anterior view, though Dietlen (22) has pictured it. We found this in only four cases in the series; in one of these it was confirmed at necropsy. Enlargement, in fact, had to be gauged with the patient in the right (I) oblique position. Regarding the structural basis for the anterior prominence in the right (I) oblique position, there is little doubt from the anatomical researches of Koch and Wieck (44) and lately of Laubry and his co-workers (51, 6) that in health it represents the stem of the pulmonary artery. With certain diseases, e.g. mitral stenosis, and also emphysema, the right ventricle in its outflow tract lengthens (42, 43, 62) and first causes prominence of the hypertrophied conus (Plate 2, Fig. 8). The question then arises how far the projection at this site, so often demonstrable in emphysema, as we have shown, is composed of conus and how much of pulmonary artery. We have had the opportunity of studying at necropsy five cases of emphysema in which photographs and drawings were made of the specimen to elucidate this point. Comparing these with the radiograms obtained in life we formed the opinion that in one the prominent arc was the conus in its lower third and the pulmonary artery in its upper two-thirds. In another the pulmonary artery accounted for the whole prominence (Plate 2, Fig. 9), and in the remaining three cases the conus took the predominant part in its formation. We have never been able in life to identify a line of junction between these two elements.

The enlargement of the 'combined' conus and pulmonary artery prominence as seen in this, the right (I) oblique, position assumed one of two forms. The more common change (24 in 33) was a rounded enlargement (Plate 2, Fig. 7). The other and less frequent type (nine in 33) was an angular enlargement (Plate 2, Fig. 10). We found that the type of enlargement, whether rounded or angular, was preserved at all degrees of rotation of the patient between 15° and 70° approximately.

It was sometimes possible to obtain certain measurements which had some value in corroborating the presence or absence of enlargement. The length of the chord formed by the combined conus and pulmonary artery shadow was taken as one measure of enlargement; the maximum depth ('flèche') of the shadow from its surface to this chord, measured vertically, provided a second criterion. Abreu (1) proposed such measurements for the pulmonary arc, though only in the anterior position. We have also applied them in the right (I) oblique position. In 28 cases the measurements could be taken from teleradiograms, and 20 of these had enlargement on inspection of the films. In these 20 the chord averaged 7.9 cm. in length, with a maximum of 9.6 cm., and a minimum of 6.1 cm. The flèche averaged 1.07 cm., with a maximum of 1.4 cm., and a minimum of 0.6 cm.

Right ventricle. It must be admitted that the signs of right ventricular

enlargement are elusive—it is a silent enlargement, even radiologically, unless it is considerable or unless it is judged in a particular way. Enlargement of the body of the right ventricle is not readily determined in the anterior position unless the degree of enlargement is considerable. In this event there is an increase in the transverse diameter of the heart, and sometimes, according to Vaquez and Bordet (77), a characteristic change in the

TABLE III

*Analysis of 80 Patients with Emphysema**Radiological evidence of involvement of the right heart and pulmonary vessels**Enlargement of right heart*

Right ventricle	18 cases
Slight	4
Moderate	10
Great	4
Right auricle	11 "
Slight	2
Moderate	9
Conus pulmonalis	33 "
Slight	9
Moderate	24

Enlargement of pulmonary artery

Slight	9	22 "
Moderate	13	

Pulmonary arc obscured by enlarged left pulmonary artery 25 "*Increased density of bifurcation of artery (in oblique positions)* 38 "*Abnormal right and left pulmonary arteries (in anterior position)* 37 "*Prominent left pulmonary artery (left (I) oblique position)* 37 "

outline of the left border, a 'sabot' effect. When enlarged, the right ventricle may sometimes take a part in forming the extreme lower part of the right border of the cardiac shadow as seen in the anterior position (22, 60), producing a 'cornered' heart, though we ourselves have only seen this in mitral stenosis and not in emphysema. The development of kymography will probably settle the point, but at present it is uncertain how commonly this occurs from enlargement; and as a guide to right ventricular enlargement in emphysema there is the additional difficulty introduced by the fact that with the low diaphragm the inferior vena cava may take a part in filling up the angle between the right cardiac border and the diaphragm.

For practical purposes the body of the right ventricle is best seen radiologically in the left (II) oblique position, where, at an angle of rotation beyond 45°, it undoubtedly forms the anterior (or sternal) border of the cardiac shadow (Plate 1, Fig. 2). A further advantage is that in this position it can be contrasted with the posterior (or vertebral) border which is as certainly the left ventricle.

In our series there was enlargement of the body of the right ventricle in 18 out of 80 cases. It was slight in four, moderate in 10, and great in four only. This enlargement, as studied in the left (II) oblique view, was reflected in an increased transverse diameter in the anterior position. In 12 this was

greater than the normal average (12.7 cm. for males, 11.5 cm. for females) and in six was greater than the normal maximum. A characteristic 'sabot'-shaped heart was never found, and with others we think that this is almost confined to certain congenital malformations with enlargement. In the left (II) oblique position the chief feature of the enlargement was the disproportion between the borders formed by the right and left ventricles. Normally the posterior border formed by the left ventricle has an equal or greater projection and curvature than the anterior border formed by the right ventricle. This relationship becomes much altered by progressive degrees of right ventricular enlargement, until the projection and curvature of the anterior border (R.V.) exceeds that of the posterior (Plate 3, Fig. 11). This criterion of enlargement is less absolute as a guide whenever enlargement of the left ventricle is present at the same time—as from hypertension. Of the 18 with right ventricular enlargement, 10 had no enlargement of the left ventricle; in all these the projection and curvature of the right ventricle was greater than that of the left. In the remaining eight both ventricles were enlarged: in six of these the enlargement was approximately of similar degree, in the other two the right ventricle was affected more. It is with bilateral ventricular enlargement that the depth of the heart in the left (II) oblique position is so strikingly increased.

Right auricle. Enlargement of the right auricle, best seen in the anterior position, was present in 11 of the 80 cases in the series. The extent to which the heart shadow projected to the right of the spine, and the length and convexity of the right border were the main criteria upon which enlargement was judged. No case in which the right auricle was affected failed to show enlargement of the right ventricle also, and (with one exception in each case) of the conus, pulmonary artery, and its branches as well. On the other hand, there was a considerable number in which these structures were abnormal, while the right auricle escaped enlargement. This is a late, perhaps the latest feature, in the cardiac changes due to emphysema. It will be expected most often when congestive failure has supervened, or in rare instances of associated auricular fibrillation. Six out of the 11 with enlargement in our series had congestive failure, to which intraventricular block had contributed in three, and bundle branch-block in one other. Of the five who had enlargement but no failure, one had auricular fibrillation, one bundle branch-block, and one other inverted T-waves in Leads II and III. Thus, there were only two examples, and in one of these the change was slight, of right auricular enlargement out of 11 in which it occurred in the series of 80 cases, where the enlargement was unassociated either with congestive heart failure or with some evidence of additional myocardial disease.

Left ventricle. Enlargement of the left ventricle was found in 25 cases. In 15 of these it was moderate, and in the remaining 10 slight.

It was pointed out in reviewing the literature that left ventricular enlargement found in emphysema was thought to be due to associated

hypertension. Kountz and his associates (45, 47), however, could find no valid explanation for such enlargement. In our series it was evident enough that there was a close connexion between hypertension and the left ventricular enlargement. Twenty-eight patients had hypertension (over 160 mm. Hg systolic, and 90 mm. diastolic), and 19 of these had enlargement of the left ventricle. To these 19, where hypertension explained the enlargement, must be added six others who also had enlargement but in whom the blood-pressure was normal.

Even in these six the explanation was not far to seek. Three of them had the unfolding of the aorta so common with hypertension, in addition to left ventricular enlargement, so that although the blood-pressure was not raised when they were seen, the combined radiological picture was that with which we are familiar in hypertension. One other had an intraventricular block, and another had inverted T-waves in Leads II and III, so that in these myocardial disease figured as a likely explanation of the enlargement. Thus, in the series there was only one example of left ventricular enlargement which could not be accounted for by hypertension or by myocardial disease. We are satisfied that when enlargement of the left ventricle occurs to an appreciable extent in emphysema, an associated or a past hypertension is the almost invariable explanation.

Left auricle. The characteristic rule in emphysema is for the left auricle to be unaffected (Plate 2, Fig. 7, and also Plate 3, Fig. 10). It was enlarged only once, and that in a patient who had auricular fibrillation based upon hypertension in addition to emphysema. One other showed a rather increased curvature of the back of the heart shadow in the right (I) oblique position, and this was confirmed by barium in the oesophagus. Here, however, the slight abnormality was most noticeable in the lower part of the curve, and as there was considerable enlargement of the left ventricle from hypertension, and also of the right ventricle, the apparent enlargement of the left auricle was almost certainly a ventricular displacement.

Vascular pedicle. The pedicle of the heart, as seen in the anterior position, was unduly wide in 16 out of the 80 cases. In four of these there was a contribution from enlargement of the superior vena cava; in these not only was the base of the pedicle involved, but in addition the right border of the shadow was continued upwards in an unduly prominent way to join the right border of the supra-aortic vascular shadow. This in turn was abnormally well seen from prominence of the right innominate vein, which here forms the edge of the shadow. Two of these four cases with enlargement of the superior vena cava had congestive heart failure at the time, and in another this was suspected.

Widening of the pedicle in the remaining cases was due to aortic unfolding. In the entire series the aortic arch was raised, lengthened, and uncoiled in 19 who had hypertension; in 13 others increased length of the pedicle and a high prominent dense aortic knuckle pointed to arteriosclerotic changes, which were confirmed by the angularity of the arch as seen in the left (II)

oblique position. It is in these cases with a long and uncoiled aorta that the translucent area in its concavity—the aortic window of the left (II) oblique position—becomes enlarged. In some emphysematous subjects with these aortic changes the window had particular brilliance, and showed up the dense left branch of the pulmonary artery which crossed it (Plate 3, Fig. 12).

Inferior vena cava. Normally the short supradiaphragmatic part of the inferior vena cava is often seen with ease when the subject is in the right (I) oblique position. In nine cases in this series it seemed to be unusually long and prominent, though probably only because of the low position of the diaphragm. With congestive heart failure no special lengthening or prominence was noticed.

The heart as a whole. The heart as a whole is not enlarged in emphysema, a fact which, to some extent, accounts for the disagreement on the presence or absence of enlargement. This study of emphysema emphasizes how different diseases affect different chambers of the heart, and that parallel enlargements of the several chambers are not to be expected in different conditions. General enlargement occurred once only in an emphysematous subject who also had auricular fibrillation and hypertension. Apart from this one example, the nearest approach to it was that six others had enlargement affecting the right ventricle and auricle and also the left ventricle. This combined change was always based upon hypertension in addition to the lung disease. So frequent is this association and so potent is it in the production of enlargement of its special kind, that this left-sided enlargement is not uncommonly seen (15 in 80 cases) as the only evidence of cardiac involvement.

Granted that the enlargement from emphysema is discriminate, it becomes important to decide its characteristic radiological form. Excluding those with hypertension or with evident myocardial disease, the enlargement is limited to the right side of the heart. It appears in the conus of the right ventricle (33 in 80), so that the anatomical evidence brought forward by Kirsch (42, 43) to show that enlargement here, of the outflow tract, has to be distinguished from the later changes in the body of the ventricle, the inflow tract, has a counterpart in life in the radiographic appearances. As a late feature the body of the right ventricle enlarges (18 in 80), but it is less common than has been thought and is rarely extreme. Those few (four in 18) who had an extreme enlargement all had congestive heart failure, with one exception. Enlargement of the right auricle is a still rarer event (11 in 80) than that of the right ventricle, and again it is almost never seen except with the supervision of congestive heart failure, or with myocardial disease, especially auricular fibrillation. Similarly the left auricle escapes enlargement entirely unless such factors complicate the lung disease. Contrasted with some other forms of heart disease, and especially with mitral stenosis and the goitre heart, the secret of this lack of obvious auricular enlargement is the rarity of auricular fibrillation in emphysema, and it has not sufficiently been taken into account in the past.

Though the size and shape of the heart may be characteristic in emphysema, it is the effects upon the pulmonary artery and its branches which are more often patent radiologically (47 in 80). In a few they formed the only changes to be recognized; and in others, unless cardiac enlargement was considerable, they overshadowed it completely.

Taking the total findings in the heart: enlargement of any kind, and also the pulmonary vascular changes, were absent in a considerable proportion of the cases (27 in 80). Age, sex, and the duration and severity of symptoms appeared to be without influence in accounting for this escape of the heart. In 18 of these the heart was normal in size and shape; in the remaining nine it was small and drop-like (Plate 3, Fig. 13). In healthy individuals with a long narrow chest the heart may look small, and this is explained (satisfactorily we think) by a more mesial placing of the heart with swinging of the apex towards the mid-line as permitted by a low diaphragm. This has often been termed a *cœur en goutte*, *Tropfenherz*, or drop-like heart. In emphysema this important factor of a low diaphragm is considerable, and the appearance of smallness would be expected even with a heart of normal size. But some have gone further and have said that the heart is literally small, smaller in fact than is normal. One explanation is advanced that the supply of blood to the heart is diminished through the reduced intra-pleural (negative) pressure, which favours relative collapse of the thin-walled superior vena cava and even auricles. Another, and we think more powerful factor, would be the diminished help given to the venous inflow owing to the absence of the natural respiratory aid it furnishes. It is not only the fixed inspiratory position of the thorax, but also the diminished pressure of the diaphragm on the liver which might so act.

Should such diminished inflow result, the total volume of the heart might be less than normal although necropsy weighing might not show decreased weight of the heart. This whole conception has been compared with the immediate result of Valsalva's experiment, i.e. a deep inspiration followed by a forced expiration with the glottis closed, and also with the reduced size of the heart reported in attacks of asthma. We have no evidence bearing directly on this point, except one case where there was no change during an attack, but we have been surprised at the rarity with which we have seen even apparent smallness of the heart in emphysema.

The heart in congestive failure. Speaking of the emphysema heart Dietlen (22) remarked that with heart failure its appearance was not materially different from that seen in failure from other causes. Certainly we cannot deny that the heart tends to enlarge as a whole with failure, so that the various enlargements characteristic of different lesions lose their distinctive features up to a point. Especially is this the case if auricular fibrillation has determined the heart failure, for then the consequent auricular enlargement completes a general enlargement of the heart that can usually be recognized easily.

Turning to the emphysema heart in our series with failure (13 in 80)

enlargement was present in all of them, and in six was considerable, but the type of enlargement remained the same in these cases with failure as in those without failure (Fig. 14). General enlargement was only found once, and that in a complicated case with hypertension and intraventricular block in addition to emphysema. One other had enlargement of the whole heart, except for the left auricle, and here again an intraventricular block was a contributory factor. In the remaining 11 there was a sharp division between those in which enlargement was based purely upon the emphysema (six in 11) and those in which hypertension was thought to have been the chief factor in producing both enlargement and failure (five in 11). In the former group the enlargement was restricted to the right heart, and was moderate in degree, except in two where it was considerable as confirmed by necropsy. In the second group, i.e. those with hypertensive changes predominant, enlargement was confined to the left ventricle.

Speaking in general terms from our small series of cases with failure, a fair statement would be that the degree of enlargement seen when failure is present is greater than in its absence. The largest hearts were found in subjects with failure (five in 80): and in these the right heart was alone affected in three out of five. Only four in the entire series had great enlargement of the right ventricle, and all of them except one had failure when first seen. Moreover, as right auricular enlargement is often found with failure (five in 11) it then adds to the degree of enlargement. The vascular changes in the lungs associated with congestive failure when this results from emphysema are like those in failure from other causes (Plate 3, Fig. 14).

Differential diagnosis. In emphysema, as we have shown, the radiographic changes are limited to an enlargement of the main pulmonary arterial tree, of the conus of the right ventricle, less often of the body of the right ventricle, and rarely of the right auricle. Unless some other cardiovascular disease is present as well, or congestive failure supervenes, other parts of the heart escape enlargement; but as the former is not infrequent, the characteristic change from emphysema alone is modified to include enlargement from these sources, especially hypertension.

Excluding these complications, the conditions which may simulate the enlargement from emphysema, therefore, are those affecting the pulmonary vessels and the right side of the heart in particular. *Mitral stenosis* is the most important, as it is the most frequent, of these. Here there is the same enlargement of the main pulmonary artery, with excessive vascularity at the hila of the lungs; and in oblique views the conus and the right ventricle partake in this enlargement. But there are many points of difference from emphysema. In anterior radiograms the aortic knuckle is often small or even absent, whereas in emphysema it is normal or prominent from age. The pulmonary arc is often much more prominent in mitral stenosis, more defined, and less likely to be obscured by the large left branch. Below the middle arc the left border of the cardiac shadow is filled in, or even projects prominently, from enlargement of the conus, a feature which we have

identified in a minor degree only four times in emphysema. The combined enlargement of the pulmonary arc and conus gives to this left border a straightened appearance foreign to emphysema, and it may so far overlap the descending left pulmonary artery as to obscure it and prevent recognition of its enlargement. The hilar vascular changes in mitral stenosis are often great—greater than in emphysema—but the main branches of the pulmonary arteries scarcely stand out radiographically so well. No doubt in emphysema their remarkable clarity is due to the over-distended lungs; but in mitral disease the sombre lung fields are related to congestion in the lung itself and perhaps to distended pulmonary veins. There is greater enlargement of the right heart in mitral stenosis than in emphysema, and it shows in anterior views therefore more often, by an increase in the transverse diameter and prominent convexity of the right border of the cardiac shadow. Right auricular enlargement is quite uncommon in emphysema unless there is fibrillation, failure, or additional myocardial disease. But the most important difference from mitral stenosis is the absence of enlargement of the left auricle. In the latter this combines with the enlarged pulmonary artery and conus in front to give to the heart a considerably increased depth, as seen in the right (I) oblique position. In emphysema the back of the heart is straight in this view, and with barium in the oesophagus the left auricular curve is normal (Plate 2, Fig. 7). We found it abnormal only twice in our series, once with auricular fibrillation and once as an artefact due to displacement by a big left ventricle. Two other emphysematous patients, seen while collecting the series but not included in it, also had an enlarged left auricle; but both of them proved later to have mitral stenosis, with a presystolic murmur on exercise which had previously been overlooked. Auricular enlargement is thus a distinctive feature of the mitral as compared with the emphysema heart, and especially in the former if fibrillation has been present for some time. But it is also a feature of fibrillation due to other causes, though auricular enlargement is then rarely so great as if mitral stenosis is present.

Congenital heart disease may lead to enlargement of the heart in a way to be differentiated from emphysema, though often the size is normal. Deformity of outline is in both more characteristic than increase in size. The pulmonary artery enlargement is often the sole abnormality, and may be great—even aneurysmal—to a degree not seen in emphysema. Excessive pulsation is often an additional and striking feature in congenital defects. The aorta may be correspondingly small. The pulmonary arc may be diminished in pulmonary stenosis, e.g. in Fallot's tetralogy, though the branches appear normal or even prominent. If the congenital heart shows enlargement, this may be general or it may specially affect the right side; a *cœur en sabot* is particularly characteristic of a congenital affection, and does not seem to result from emphysema.

A general rather than particular enlargement is the characteristic of the *goitre heart* and of the heart in *myxoedema*. In the former, difficulty would only arise in distinguishing from the effects of emphysema when the

pulmonary artery alone is affected, as it often is. It is then prominent in the same way in anterior views, but it is often freely pulsatile though with branches not specially prominent as in emphysema. Enlargement of the conus is rarely seen, even in the right (I) oblique position.

Enlargement of the heart from *endarteritis of the pulmonary vessels*, whether syphilitic or not, bears the closest resemblance to that in emphysema, but it is rare. There are the same vascular changes in the lungs, and the same selective enlargement of the pulmonary artery and right side of the heart. If there is a radiological distinction between the two it lies in the excessive pulsation of the pulmonary vessels described as usual in pulmonary endarteritis, in the high degree of enlargement of the right heart, and in the presence of an underlying pulmonary lesion so commonly associated.

Summary

Eighty patients suffering from a high grade of emphysema were investigated, chiefly in regard to the cardiovascular system, and in particular to the size and shape of the heart as judged by radiology.

The cardiac factor in emphysema alone is seldom pronounced except late in the disease, and then not always, or unless there is also a cardiac lesion of another sort. A complicated aetiology is so common that it was demonstrable in more than half of this series, and the complication was predominantly hypertension. It may be said that cardiac symptoms and signs in emphysema are more likely to be due to hypertension than to the direct effect of emphysema on the heart.

Clinical evidence is an uncertain guide to involvement of the heart in either pure emphysema or when this is combined with other cardiovascular disease. Cardiac and pulmonary symptoms are similar; and the physical signs in emphysema indicative of a cardiac element are admittedly scanty. In particular there is no guide to cardiac enlargement, and as this is a proof that the heart is implicated we are dependent on radiology, except in late examples where oedema is proof enough that the heart is involved. Electrocardiographic evidence is disappointing, for there is right ventricular predominance in a small proportion only; its chief value is to provide other evidence of a complicating myocardial (coronary) disease, e.g. a bundle branch lesion.

The most frequent and radiological change in the cardiac involvement of emphysema is enlargement of the branches of the pulmonary artery at the hila (about 46 per cent.), with or without enlargement of the main stem (about 58 per cent.). In the anterior view the enlarged pulmonary or middle arc is sometimes obscured by its large left branch. Localized enlargement of the heart is the second main proof that the heart is implicated in emphysema, and it is demonstrable in over one-third (about 40 per cent.). It concerns most often the conus pulmonalis of the right ventricle (about 41 per cent.), and in about half these the body of the right ventricle also, best

seen in the left (II) oblique and right (I) oblique positions respectively. Enlargement of the right auricle is not common (about 14 per cent.).

Enlargement of the left ventricle (about 30 per cent.) and of the left auricle (about 1 per cent.) is dependent upon the co-existence of other cardiovascular disease, for in pure examples of emphysema it does not occur, unless, perhaps, in the late stage of congestive failure. Systemic hypertension is the almost invariable cause of the left ventricular enlargement when this is found; a few others have myocardial (coronary) disease, e.g. with bundle branch-block. Enlargement of the left auricle was found once only, and that in the sole instance of auricular fibrillation. The infrequent enlargement of the right auricle and the rare enlargement of the left auricle can be related to the freedom from auricular fibrillation and to the admitted rarity of failure at all from emphysema alone.

The heart as a whole is not enlarged in uncomplicated cases of emphysema. Great enlargement of the right heart is rare, being seen in four only. In none of these was there a sabot appearance. About one-third of patients have no enlargement at all and no changes in the pulmonary vessels radiologically. The small and drop-like heart shadow, though so often held to be characteristic of emphysema, is in our experience only seen occasionally.

These results from the use of X-rays now permit recognition in life of the features of enlargement long known to morbid anatomists. They go further in that most of these traditional records are largely diminished in value by the inclusion of unrecognized hypertension or myocardial disease in association. In pure emphysema it is the outflow tract of the right ventricle (Kirsch) extending from the apex to the pulmonary artery, which is earliest affected by enlargement and manifested by prominence of the conus. Later the body of the right ventricle is also involved, and this is represented by right ventricular prominence in the left (II) oblique position. These are the changes in the heart characteristic of pulmonary hypertension. Cardiac failure from emphysema alone is surprisingly rare; and when it occurs it is with normal rhythm and oedema, and as a very late event that is almost invariably terminal. Recurrent bouts of failure are almost unknown. Examples of failure apparently due to emphysema are most often explained by associated cardiovascular disease, usually hypertension, and in such, failure can be recurrent. The differential diagnosis, especially from mitral stenosis, congenital heart disease, and the goitre heart is briefly discussed.

We wish to thank the staff of the London Hospital and of the National Hospital for Diseases of the Heart, especially Dr. Cecil Wall, Dr. Donald Hunter, Dr. Cotton, and Dr. Evan Bedford, and also the Medical Superintendents of St. Olave's and Sidcup Hospitals, for permitting us to include cases under their care. The work by one of us (C. H.) was done partly under the tenure of the Paterson Bequest.

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DESCRIPTION OF PLATES

FIG. 1. Normal chest. Anterior view. Healthy woman, aged 40.

FIG. 2. Normal chest. Left (II) oblique view. Healthy man, aged 31. Showing right and left cardiac borders, and the left pulmonary artery crossing the aortic window below the aortic arch.

FIG. 3. Normal chest. Right (I) oblique view. Healthy woman, aged 45. Showing the normal slight convexity of the cardiac outline in the region of the pulmonary artery.

FIG. 4. Emphysema. Anterior view. Man, aged 45. Post-mortem control. Showing prominent and lengthened middle arc on the left from enlargement of the stem of the pulmonary artery. In addition, the branches of the pulmonary artery are wide and dense (increased hilar shadows).

FIG. 5. Emphysema. Anterior view. Man, aged 50. Showing the right and left branches of the pulmonary artery enlarged, yet without prominence of the main pulmonary arc.

FIG. 6. Emphysema. Left (II) oblique view. Man, aged 64. Showing wide and dense left pulmonary artery below the aortic arch.

FIG. 7. Emphysema. Right (I) oblique view. Man, aged 45. Post-mortem control. Showing dense shadow of enlarged pulmonary artery, denser than the aortic arch above it, and producing (with the left bronchus) a pulmonary artery curve on the oesophagus. The enlarged right pulmonary artery is seen running backwards to the spine.

FIG. 8. Emphysema. Photograph of heart *post mortem*. Man, aged 38. Showing right ventricular enlargement, the right ventricle forming the apex, and showing the lengthening and prominence of the conus region. The undue lengthening of the outflow tract from apex to pulmonary artery is noteworthy.

FIG. 9. Emphysema. Photograph of heart *post mortem* in the restored right (I) oblique view. Man, aged 49. Showing the long and prominent border of the pulmonary artery below the aortic arch and to the right (front).

FIG. 10. Emphysema. Right (I) oblique view. Man, aged 50. Showing angular prominence on the anterior border due to enlargement of the conus and pulmonary artery. The dense shadow of the dividing pulmonary artery is seen nearer the spine.

FIG. 11. Emphysema. Left (II) oblique view. Man, aged 70. Showing undue convexity on the right from enlargement of the right ventricle, and pronounced widening and density of the left pulmonary artery passing backwards to the spine below the aortic arch. The aortic window is largely obliterated by it.

FIG. 12. Emphysema. Left (II) oblique view. Man, aged 69. Showing increased space and brilliance of the aortic window across which runs the left pulmonary artery, and lower still the pulmonary veins to enter the left auricle. The aortic triangle is also exaggerated from emphysema.

FIG. 13. Emphysema. Anterior view. Man, aged 45. Showing drop-like mesial heart and low diaphragm.

FIG. 14. Emphysema. Heart failure. Anterior view. Man, aged 35. Post-mortem control. Showing excessive pulmonary vascularity, old adhesions at right base, and widening of the cardiac shadow from enlargement of the right auricle and right ventricle.

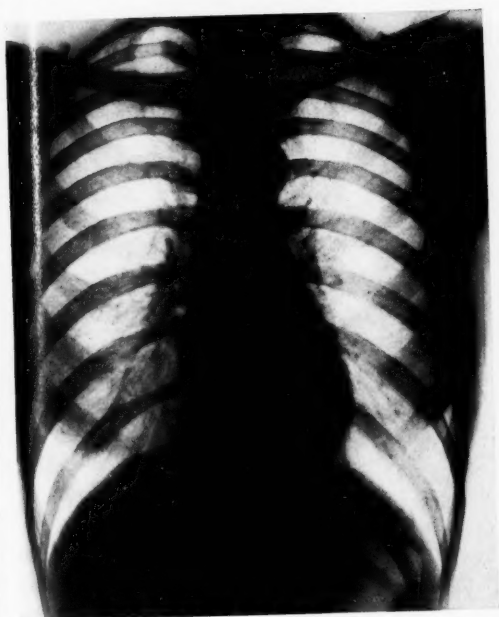


FIG. 1



FIG. 2



FIG. 3



FIG. 4

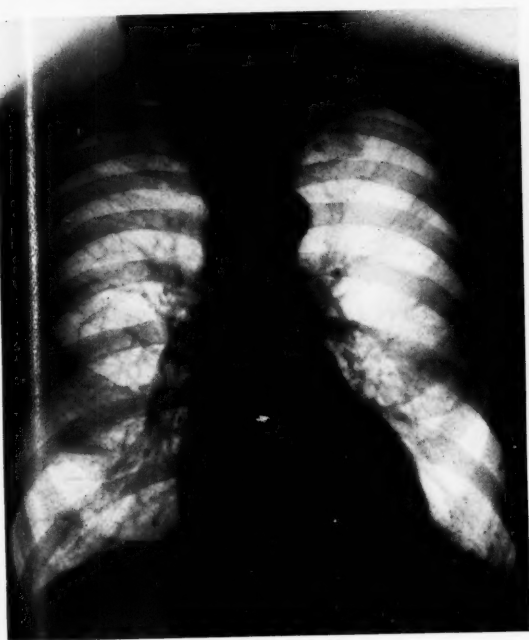


FIG. 5



FIG. 6

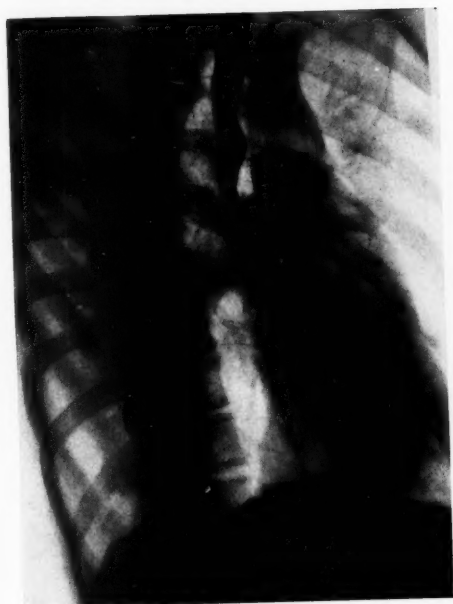


FIG. 7



FIG. 10



FIG. 8



FIG. 9

Quart



FIG. 11



FIG. 12

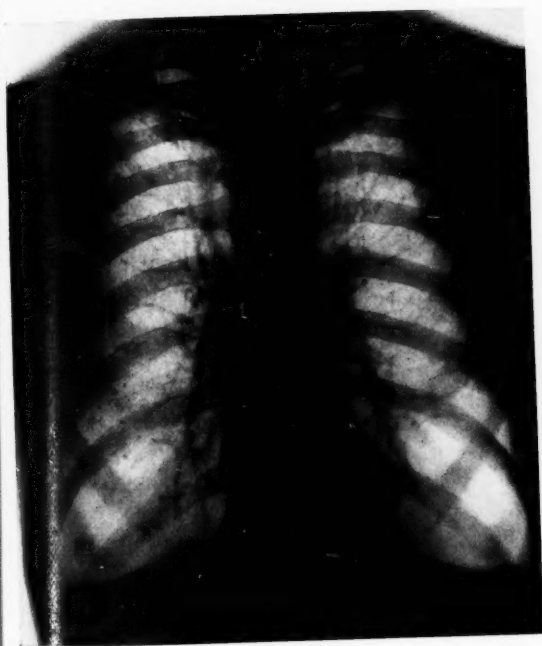
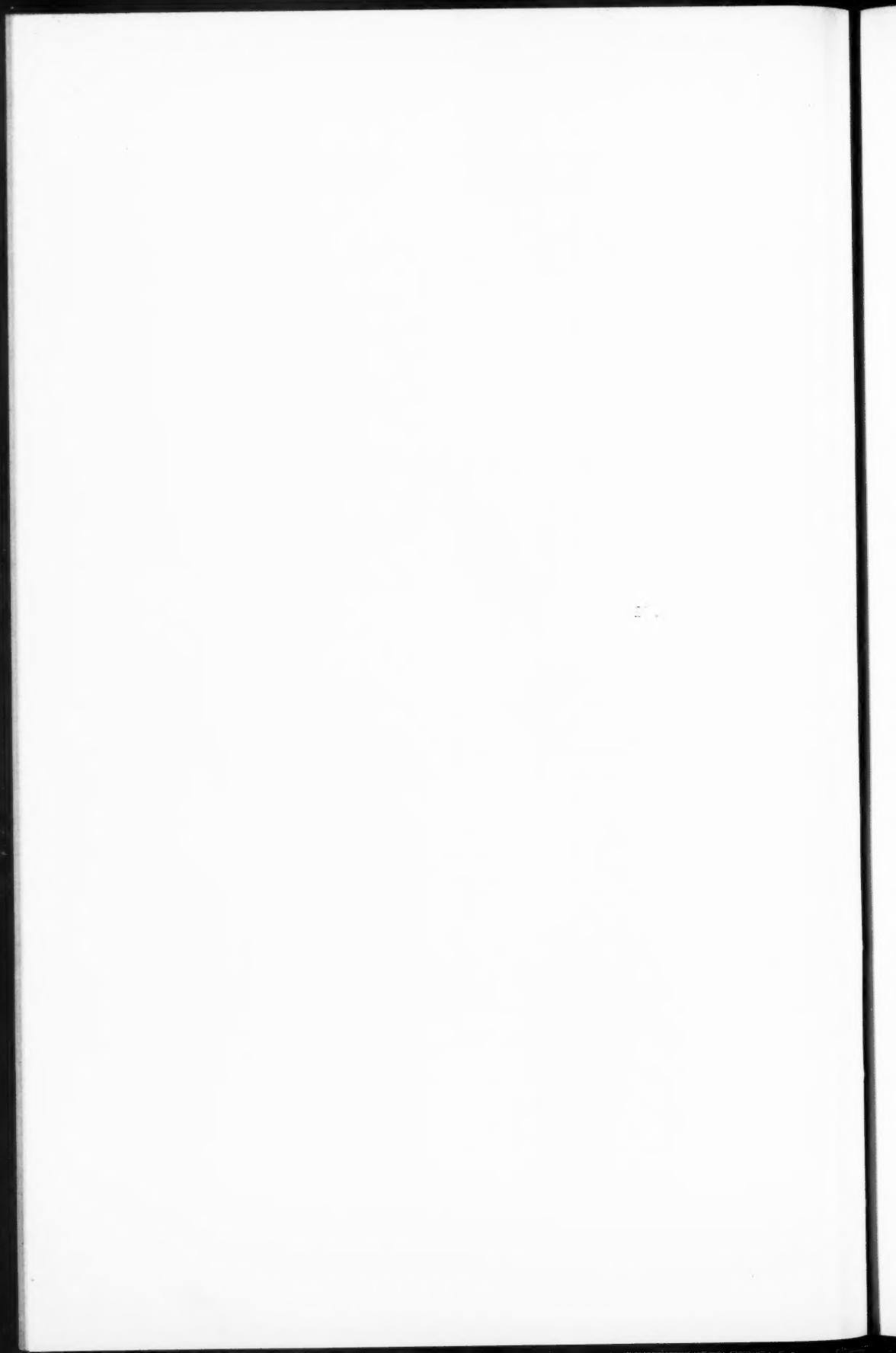


FIG. 13



FIG. 14



THE MAGNESIUM CONTENT OF SERUM IN RENAL INSUFFICIENCY¹

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SINCE the studies of Loeb (1) on the synergism and antagonism of ions much evidence has accumulated to show that the several inorganic constituents of the body influence each other profoundly, both in relation to their absorption, retention, and elimination, and to their relative amounts in the tissues and body fluids. The observation by Meltzer and Auer (2) that animals narcotized by the injection of magnesium sulphate could be rapidly restored to normal by the injection of a calcium salt led to the recognition of the existence of an important relationship between the calcium and magnesium ions, but its significance in physiological and pathological processes is still far from being satisfactorily elucidated. The discovery by the writer (3, 4) of an inverse relationship between the calcium and magnesium in the serum of the rabbit under certain conditions naturally stimulated inquiry as to whether such a relationship could be demonstrated in the human subject. The finding of Hirschfelder (5) that the serum magnesium figure was often considerably raised in the presence of renal inadequacy seemed to indicate a profitable field for the study of any relationship which might exist in patients. Furthermore, since Hirschfelder asserts that an important cause of coma in renal disease is excessive administration of magnesium sulphate, some of which is absorbed, but not sufficiently rapidly eliminated, it was obviously of importance to try to repeat his observations.

Accordingly, estimations of serum calcium and magnesium were made in a series of patients with well-marked renal inadequacy, as judged by clinical criteria and renal function tests. The serum inorganic phosphorus was also studied, in view of its known relationship to the serum calcium in other conditions and its significance as a guide to the degree of renal insufficiency. In addition, determinations of the three constituents were made at intervals after the oral administration of magnesium sulphate. The Kramer-Tisdall technique (6) was employed for the calcium determinations. Magnesium and inorganic phosphorus were estimated in accordance with the procedure of Briggs (7), modified in the particulars outlined in an earlier paper (3).

I. *Serum calcium, magnesium, and inorganic phosphorus in renal inadequacy.* The results of 23 observations on 21 subjects, all adults, are recorded in Table I. They are arranged under headings according to the clinical

¹ Received November 12, 1936.

TABLE I

Cases of Renal Insufficiency

Case No.	Age.	Sex.	Calcium mg. per 100 ml. serum.	Magnesium mg. per 100 ml. serum.	Inorganic phosphorus mg. per 100 ml. serum.	Non-protein nitrogen mg. per 100 ml. serum.	Clinical data.
<i>Glomerulo-nephritis.</i>							
1	18	F	8.6	2.05	4.13	50	Chronic type
2	25	M	10.2	2.21	6.27	90	Chronic type
3	30	M	6.4	2.44	6.68	62	Subacute type
4	27	M	9.4	2.67	4.20	42 (serum)	Acute diffuse type
5	28	F	6.1	2.75	17.85	212	Chronic type. Coma
6	24	F	8.0	2.79	5.95	75	Acute diffuse type
7	33	M	6.5	2.89	19.85	200	Chronic type
8	21	M	6.5	2.85	8.41	70	Subacute type
			6.2	3.06	28.02	136	10 months later. Coma
9	54	F	8.3	3.09	8.21	132	Chronic type
10	52	M	10.0	3.28	6.87	68	Chronic type
<i>Nephrosclerosis.</i>							
11	72	F	8.4	2.18	3.13	54	—
12	67	F	8.1	3.56	9.52	200	Coma
<i>Enlarged Prostate.</i>							
13	77	M	8.9	2.22	3.03	59	—
14	70	M	8.2	2.30	4.76	72	—
15	80	M	8.5	2.46	3.88	94	—
16	61	M	9.1	2.49	7.52	128	—
			8.9	3.39	8.50	125	1 month later
17	71	M	8.1	3.33	13.60	130	—
<i>Diabetes.</i>							
18	60	M	8.0	3.59	6.38	143	Coma
19	65	F	9.3	3.93	6.87	—	Coma
20	45	F	7.3	2.83	6.87	72	Pregnancy kidney, accidental haemorrhage
21	18	F	7.4	3.01	12.31	286	Bilateral pyonephrosis

diagnosis, the bulk of the cases falling into two groups, viz., glomerulo-nephritis and renal inadequacy consequent on prostatic enlargement. Many of the patients had been receiving average doses of magnesium sulphate for therapeutic purposes. A series of control estimations was done on nine patients suffering from a variety of chronic conditions in which any disturbance of mineral metabolism could be excluded with reasonable confidence. The calcium figures so obtained varied from 8.0 to 10.8, the average value being 9.1 mg. per 100 ml. The magnesium figures were remarkably uniform, the range being 1.89 to 2.19 with an average value of 2.04 mg. per 100 ml. Regarding these figures as representing normal values, it will be seen that in the severer cases of glomerulo-nephritis there is an elevation of the serum magnesium figure, which is some 50 per cent. greater than the normal. As is usual in this type of nephritis the calcium figure is markedly depressed, while the serum inorganic phosphorus is increased, roughly proportionately to the non-protein nitrogen value. In some of the enlarged prostate cases

TABLE II

Oral Administration of Magnesium Sulphate

Case No.	Age.	Sex.	Amount of magnesium sulphate.	Time.	Calcium mg. per 100 ml. serum.	Magnesium mg. per 100 ml. serum.	Inorganic phosphorus mg. per 100 ml. serum.	Non-protein nitrogen mg. per 100 ml. blood.	Diagnosis.
2	25	M	1 oz. in 6 fl. oz.	Before	10.2	2.21	6.27	90	Chronic glomerulo-nephritis
				1 hr. after	8.6	2.36	6.27		
				3 hrs. after	8.9	2.54	6.44		
				6 hrs. after	9.3	2.56	6.27		
6	24	F	1 oz. in 6 fl. oz.	Before	8.0	2.79	5.95	75	Acute diffuse glomerulo-nephritis
				1 hr. after	8.2	2.89	5.95		
				2 hrs. after	8.3	2.92	5.99		
				8½ hrs. after	8.2	2.59	6.21		
10	52	M	1 oz. in 8 fl. oz.	Before	10.0	3.28	6.87	68	Chronic glomerulo-nephritis (vomited after ¾ hr.)
				1 hr. after	10.9	3.70	7.36		
				3¼ hrs. after	11.3	3.56	7.36		
16	61	M	½ oz. in 1 fl. oz.	Before	8.9	3.39	8.50	125	Enlarged prostate
				¾ hr. after	8.7	4.04	8.50		
				1½ hrs. after	8.6	5.26	8.50		
				3½ hrs. after	8.3	4.88	8.50		
21	18	F	½ oz. in 5 fl. oz.	Before	7.4	3.01	12.31	286	Bilateral pyonephrosis
				1 hr. after	7.5	2.36	12.76		
				2½ hrs. after	7.0	2.33	12.99		
				8 hrs. after	6.8	2.18	12.76		

still higher magnesium values are encountered, the increases being some 70 per cent. above the normal. In these groups the calcium figure is only slightly depressed.

II. *Serum calcium, magnesium, and inorganic phosphorus following the oral administration of magnesium sulphate.* In Table II five series of observations are recorded in which patients with renal impairment received large doses of magnesium sulphate. In each instance blood was taken and then ½–1 ounce of magnesium sulphate administered, dissolved in a small volume of water in order to delay the cathartic effect and to promote absorption. Further blood samples were taken at suitable intervals, the patient being kept in a fasting condition throughout.

It will be seen that in four of the cases there is a rise in the serum magnesium, attaining its maximum in two to three hours. In one case (No. 21), notwithstanding the existence of marked renal impairment, there was a definite fall. The serum calcium fell slightly in three cases, remained practically constant in one (No. 6) and rose in the remaining case (No. 10). As this man vomited ¾ hour after taking the magnesium sulphate it is probable that he absorbed less of the salt than he might otherwise have done. Case 16 is noteworthy in that here, where the rise in the magnesium value is more uniform and marked, there is an almost equally marked fall in the serum calcium value. In this particular instance there would appear to be a definite inverse relationship between the magnesium and calcium,

but in the other cases, where the changes in the magnesium figure are comparatively slight, the existence of any relationship between the calcium and magnesium is problematical. In some of the cases a slight rise in the serum inorganic phosphorus is observed.

Discussion

The relationship between serum calcium and magnesium. The finding of an inverse relationship between the serum magnesium and calcium in the rabbit has already been referred to. There are obvious difficulties in detecting the presence of such a relationship in man. In contrast to the rabbit the normal values in the human subject lie within narrow limits and their resistance to change by experimental methods renders the detection of the relationship a somewhat uncertain matter. Moreover, in controlling the level of the serum calcium especially, other factors are at work so that any relationship existing between the serum calcium and magnesium will be readily masked. On the whole, the observations recorded above lend support to the existence of the inverse relationship in man, and, if a fall in the serum calcium is a frequent finding in renal inadequacy, a rise in the serum magnesium would appear to be equally common. Further, in the one case where a substantial rise in the serum magnesium was produced by the oral administration of magnesium sulphate, the fall in the serum calcium was definite and uniform.

The serum magnesium level in renal inadequacy. The serum magnesium values in the present series of cases range from 2.05 to 3.93 mg. per 100 ml., the highest value being encountered in a fatal case of diabetes in which renal failure played a prominent part. Observations on the serum magnesium in nephritis, often incidental to other studies, have been recorded by a number of workers previously. Denis and Hobson (8) found a range of 2.2 to 2.9 mg. per 100 ml. in 19 cases, Salvesen and Linder (9) a range of 1.5 to 4.6 mg. per 100 ml. in 15 cases and Rabinowitch (10) a range of 2.0 to 3.1 per 100 mg. in 20 cases. More recently Becher and Hamann (11) reported values ranging from 2.7 to 5.7 in a group of 10 cases, each with a very high non-protein nitrogen level. Their three highest figures were, however, obtained on blood which was taken after death, where the possibility of the diffusion of magnesium from the tissues has to be considered. Walker and Walker (12) observed a raised serum magnesium level in five cases of hypertension with renal damage, their highest value being 4.2 mg. per 100 ml. Cope (13), in a study of the blood changes which follow the intensive administration of alkalis, found that in five subjects who exhibited signs of alkalosis the serum magnesium was considerably raised, and in one instance reached a level of 6.84 mg. per 100 ml. In each case there was a high blood urea value. In four cases of renal inadequacy due to nephritis, which presented comparable blood urea figures, the serum magnesium did not rise above 3.25 mg. per 100 ml. Cope ascribes the high magnesium

figures in the presence of alkalosis to absorption from the alkaline powders of magnesium which could not be eliminated subsequently with sufficient rapidity by the damaged kidneys. A very high magnesium figure, 10.34 mg. per 100 ml., has been reported by Watchorn and McCance (14) in a case of uraemia.

The results of Hirschfelder (5), which have already been referred to, include three very high figures, namely 8.93, 9.0, and 13.0 mg. per 100 ml. respectively. This writer further reports exceptionally high values after the administration to nephritics of 20 grammes of magnesium sulphate by mouth. Of ten such cases cited, nine had a magnesium figure greater than 7.75 mg. per 100 ml., the highest value observed being 16.5 mg. per 100 ml. Hirschfelder related the height of the serum magnesium to the degree of drowsiness of the patient and concluded that hypermagnesaemia was an important causal factor in many cases of so-called uraemic coma.

Both the present investigation and the various series previously reported by other workers have included cases of very severe renal inadequacy. Many of these cases must have been receiving large doses of magnesium sulphate in order to encourage nitrogen elimination by the intestine, and yet with only one exception can it be said that the magnesium figure approached the level at which magnesium narcosis might be regarded as an important factor in the production of coma.

The balance of evidence would seem to suggest therefore that, except under very special circumstances, magnesium salts can be administered without undue apprehension in those cases of nephritis where they are otherwise indicated.

Summary

1. Serum calcium, magnesium, and inorganic phosphorus values are reported in a series of twenty-one cases of renal inadequacy of different types.

2. An increase in the serum magnesium has been found to occur almost invariably as a result of renal dysfunction, but in the present series the increase has not exceeded double the normal value.

3. Evidence pointing to the existence of an inverse relationship between the calcium and magnesium of serum is adduced.

4. The oral administration of magnesium sulphate to five subjects with renal disease caused a slight and inconstant rise in the serum magnesium.

The writer wishes to record his indebtedness to Dr. J. P. Steel, Medical Superintendent of Smithdown Road Hospital, for providing facilities for the investigation of the majority of the cases forming the subject of this report.

The expenses of the work were defrayed out of a grant from the Medical Research Council, to which acknowledgement is made.

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TREATMENT OF ACUTE RHEUMATIC POLYARTHRITIS WITH CONCENTRATED ANTISCARLATINAL SERUM¹

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Introduction

THIS study of the action of antiscarlatinal serum in rheumatic polyarthritis and chorea was begun five years ago as the result of a growing dissatisfaction with the immediate and remote results of the use of salicylates. By now some sixty cases of 'rheumatism' have been treated, and the present communication deals with all our cases of acute rheumatic polyarthritis to the number of forty-one, three of which were controls. Few investigations could present more difficulty than that of assessing the value of a therapeutic measure in a disease in which the principal danger is from its remote sequelae, but it is felt that sufficient material has accumulated to warrant the presentation of a detailed study. Preliminary communications have already been published (1, 2).

Present Position of Salicylate Therapy

Following the introduction, by MacLagan (3), in November 1874, of salicin, and independently by Stricker (4) and Reiss (5), in 1885, of sodium salicylate, in the treatment of acute rheumatic fever, the latter remedy came rapidly and widely to be regarded as a specific drug with absolute curative properties. Indeed, 'many regard it as such to-day, but on slender evidence' (6). It has, however, hitherto been justifiably accepted by the general body of the medical profession that 'on the whole, the salicylates in acute rheumatism have a more prompt, regular, and satisfactory effect than any other drug or drug combination, and for that reason they remain unquestionably the remedy of choice' (6).

In assessing the value of any new therapeutic measure it is quite natural that our measure of its success should be by comparison with the results given by the method of treatment already in accepted use. An examination of the present position of salicylate therapy has therefore been carried out.

In 1880, some six years after its introduction, Vulpian (7) pointed out the inability of the new therapy to prevent cardiac sequelae, and the validity of his observation is above question. It has been contended (White (8), Lees (9), Coombs (10), Miller (16)) that if salicylates cannot prevent, at least they can lower the incidence of rheumatic heart disease. There is a

¹ Received September 24, 1936.

more considerable body of evidence and opinion (Leech (11), Perry (12), Ehrstrom and Wahlberg (13), Master and Romanoff (14), Bezançon and Weil (15), &c. (17)) that salicylates in no way influence the incidence or the course of cardiac rheumatism. Moreover, it is unlikely that salicylates shorten the necessary period of recumbency and convalescence—and hence of hospitalization. (Miller (18), Fantus (19), Master and Romanoff (14), &c. (20).) Statements, common in textbooks (e.g. Horder (21) that 'a patient suffering from an acute polyarthritis who is not considerably better after 48 hours of salicylates is almost certainly not suffering from rheumatic fever'), might convey the impression that salicylates enjoy success in each and every case of rheumatic polyarthritis. Such an impression would be erroneous. Hanzlik's (22) study of the action of salicylates in acute rheumatic polyarthritis gave 16.5 per cent. partial failures and 1.5 per cent. complete failures, while in subacute rheumatic polyarthritis (fitting joint pain and swelling, but no fever) there were 30 per cent. partial failures and 17 per cent. complete failures. A disappointingly high proportion of unsatisfactory responses to salicylate treatment led Miller (18) to seek a more reliable therapeutic agent. It is now generally conceded that a small proportion (1 to 2 per cent., Hanzlik, Lyon (22, 23)) of cases of acute rheumatic fever are completely resistant to the most adequate salicylate therapy, but the examination of such a series as that presented by Lyon (23) shows there has probably been a good deal of careless condemnation of the power of salicylates to influence rheumatic fever favourably. In 95 per cent. of those cases which failed to respond to treatment, the dosage of salicylates was unsatisfactorily low; no reason was given for the inadequate dose in those cases which failed to respond, but we would suggest that the usual cause in cases treated in hospital is neither ignorance nor carelessness, but the clinical difficulties in the way of maintaining a full dose. Intolerance to salicylates, especially on the part of the gastro-intestinal system, is frequently so marked as to be a bar to effective therapy, and renders a low dose an absolute necessity. Hanzlik (22) stated that for 90 per cent. of adults the toxic dose of salicylate of soda lies between 100 and 200 gr. daily, which is approximately the range of dosage necessary in acute rheumatism. In considering the enormous consumption of the drug the accident rate is low, but every year a few fatal reactions are reported in the literature, and it is safe to assume that a number remain unpublished.

As a certain number of relapses have occurred under the serum treatment about to be described, attention must be given to salicylate relapses. In Lyon's (23) series, 38 per cent. of 100 patients showed fifty-eight relapses in all, most of them referable to reduction of dosage when pain and fever remitted. But when the dose of sodium salicylate was maintained at 120 gr. daily only 3 per cent. relapsed. Possibly in many cases salicylate dosage is lowered in order to relieve evidences of intoxication by the drug, thus increasing the danger of relapse.

The *immediate* results of our standard therapy thus being far from entirely

satisfactory, there is every justification for the search for a more reliable immediate therapeutic agent. It is admitted that the serum treatment now described has certain disadvantages (e.g. longer fever and serum rash) as compared with the standard therapy, but these disadvantages are fully compensated by the absence of symptoms of salicylism (headache, vomiting, acid and pungent sweats). In this study evidence is presented that serum has immediate effects which are at least as good as with salicylates.

An even stronger justification for the search for a more effective anti-rheumatic agent lies in the mortality and disability rates in the years following acute rheumatism. Over 50 per cent. of cases of rheumatic manifestation in children are followed by death or cardiac decompensation within ten years (Wallace (66)). It is too early yet to assess the possibility of serum preventing results so disastrous, but it is submitted that there is every justification for a widespread experiment with serum therapy by members of the profession

The Rationale for the Use of Concentrated Antiscarlatinal Serum

In 1931 a patient came under observation who had suffered from joint pains and fever for ten months, and who did not react to an average dose of 90 gr. of sodium salicylate given daily over a period of three weeks. A 'course' of serum produced a complete remission of pain and fever within twenty-three days, and no further treatment of any kind was employed. This case marked the inception of the present series.

The decision to employ concentrated anti-scarlatinal serum was influenced by the growing mass of evidence as to the intimate relationship between acute rheumatism and the streptococcus. Since 1931 the weight of this evidence has considerably increased.

Haig Brown (24), as physician to Charterhouse School, was the first to associate tonsillitis and rheumatic fever. Since then Dudley (25) has demonstrated the relation between haemolytic streptococcal tonsillitis and acute rheumatism in the boys of the training ship *Impregnable*. Glover and Griffith (26, 27) have borne out this relationship in streptococcal infections in boys in the R.A.F. at Halton; while Bradley (28) has determined the same relationship in an epidemic of haemolytic streptococcal tonsillitis occurring in a school. At the end of last century Longstaffe (29) demonstrated the statistical relationship between the incidence of scarlet fever, puerperal fever, and rheumatic fever in the general population. More recently Wallace and Smith (30) have studied a similar association in Edinburgh in a recent wave of streptococcal infection. As compared with preceding years, in 1934 and 1935 the notification rate of scarlet fever increased by 350 per cent. of the average normal figure. In the same period the number of admissions to the Royal Infirmary in Edinburgh for rheumatic fever increased by 50 per cent. of the average figure. Mastoiditis and erysipelas were similarly increased. Sheldon and Collis (33, 34) in Britain, and Coburn and Pauli (35, 36) in America have made routine studies of the throat

flora in rheumatic subjects (i.e. children with a history of recurrent attacks of rheumatism), and both groups of workers have submitted convincing evidence that only haemolytic streptococcal infection will precipitate rheumatic manifestations in such individuals. Non-haemolytic streptococci and other organisms are not effective. Coburn and Pauli (37) have studied strains of effective streptococci and show that not only have all effective

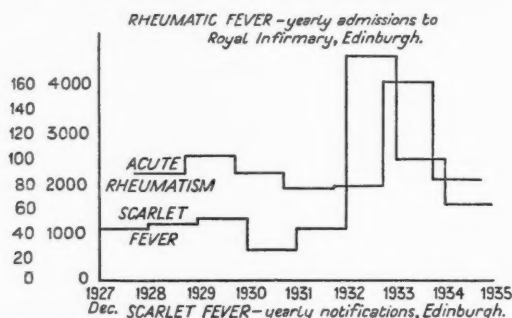


FIG. 1. Exact correlation in time between these two graphs is not possible as the statistical year in the hospital ends in September, while in the city it ends in December.

strains a capacity for producing an erythrogenic (skin reddening) toxin, but also they have other cultural characteristics in common with the scarlatina streptococcus of Dick.

In addition there is a large body of indirect evidence derived by workers from the antibody contents of blood in acute rheumatism. Todd (31), Coburn and Pauli (36, 37), Myers et al. (32), have shown increased antistreptolysin content; Griffiths (38) showed increased antihemolysin; and Hadfield et al. (39) showed an increased antistreptococcal fibrinolysin. However, more recently Schlesinger et al. (40) conclude that while in many cases antistreptococcal precipitins are raised, acute rheumatism can occur without significant departure from the normal level. Wilson (41) has criticized results obtained with antistreptolysin on similar grounds. Evidence derived from skin sensitivity reactions are unsatisfactory, as Birkhaug (42) has demonstrated that normal skin is sensitive to toxins from many different kinds of streptococci, and evidence accumulated on the basis of skin reactions may be largely discounted.

In conclusion, evidence of the association between haemolytic streptococci and rheumatism is quite strong enough to prompt the experimental use of antistreptococcal serum, while particular details of the evidence would indicate the antiscarlatinal serum as the most suitable.

Serum and its Administration

A stock concentrated antiscarlatinal serum (P. D. & Co.) was used throughout. All patients were tested for serum sensitivity by intradermal injection of 0.2 c.c. of a 1 in 10 dilution of serum. Positive results were indicated by

a red flare, sometimes with a central wheal. Non-sensitive patients received 30 c.c. (one phial) of serum intramuscularly (gluteus maximus), and this dose was repeated in thirty-six hours. This dose was equivalent to 18,000 new units of antitoxin (New York State Board), or to 900,000 old Dick units. It contained about 12 gm. of pseudo-globulins, with practically no albumin or euglobulin. (Information by the courtesy of P. D. & Co., Scientific Department, Detroit.) Sensitive patients were desensitized by the following method: 0.02 c.c. was given subcutaneously as the initial dose and this dose was doubled each half-hour until 2 c.c. had been given; the remaining volume of the 30 c.c. dose was given as 8 c.c. and 20 c.c. intramuscularly at half-hour intervals. All patients requiring a second course of serum were treated in the same manner without preliminary skin testing.

A number of patients received intramuscular serum in other than the routine method of dosage. Some patients were so ill with carditis on admission that it was deemed unwise to expose them to the full 30 c.c. at once. The various cases are analysed below. It may be said that the method of administration of the dose did not seem greatly to influence its ultimate success, and it is mainly the convenience of the above method that determined its continuation as the method of choice.

In presenting case histories, two doses of 30 c.c. of serum intramuscularly will be termed a 'routine course' of serum.

Protocols

Cases are presented in three groups. First come those in which the rheumatism was treated entirely without salicylates; secondly, a group in which salicylate therapy had already been used; and thirdly, a group in which for one reason or another salicylates were given after the injections of serum. It has to be admitted that many cases of acute rheumatism are self-limiting and of short duration after admission to hospital; each group has therefore been divided into cases of short duration and cases continuing for over three weeks. Spontaneous recovery within a brief period of entry into hospital in cases of duration of over three weeks is not common.

1. Cases Treated Without Salicylates

A. Cases of less than three weeks' duration.

1. Female, aged 16. Acute rheumatic polyarthritis, duration six days, preceded by sore throat. Previous frequent sore throats, no other rheumatic manifestation, and heart apparently normal on admission. Given one routine course of serum; four days later developed serum rash lasting one day; afebrile seven days after serum. Out of bed fifty-nine days after serum, discharged with remark 'heart-sounds seem healthy'. Reported three years later with evidence of early mitral stenosis, but no further joint rheumatism.

2. Female, aged 10. Acute rheumatic polyarthrititis, duration ten days. Previous occasional sore throats. Heart damaged when admitted. Given one routine course of serum; seven days later developed rash of three days' duration; afebrile six days after serum. Allowed up fifty-three days after serum. On discharge heart as on admission. Reported two years later, heart unchanged, but no further rheumatism.

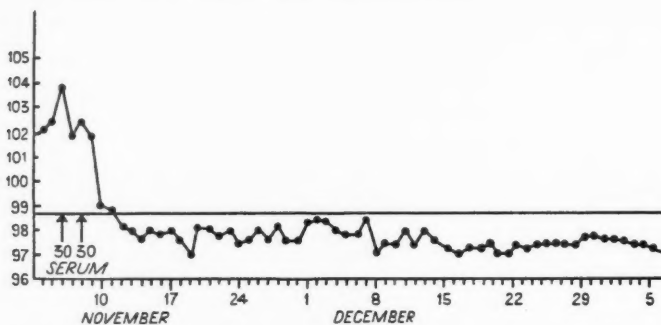


FIG. 2, Case 2. Daily maximum temperature.

3. Female, aged 16. Acute rheumatic polyarthrititis, duration six days, preceded by sore throat. Previous history of rheumatism after scarlet fever. Heart normal on admission. Given one routine course of serum. No rash. Afebrile six days later. Allowed up fifteen days after serum. No evidence of cardiac damage sixteen months after serum.

4. Female, aged 31. Acute rheumatic polyarthrititis, duration eight days, preceded by sore throat. No previous history of rheumatism, but mitral stenosis and incompetence present on admission. Given one routine course of serum. Eight days later rash (duration one day) developed. Afebrile thirteen days after serum. Allowed up thirty-five days after serum. Sixteen months later heart as on admission, with no further evidence of rheumatism.

5. Female, aged 15. Acute rheumatic polyarthrititis, duration three days, preceded by sore throat. Previous history of frequent sore throat and growing pains, but heart normal on admission. Given one routine course of serum. No rash. Afebrile seven days after serum. Discharged fifteen days after serum, with no evidence of cardiac damage.

6. Female, aged 16. Acute rheumatic polyarthrititis, duration eight days, preceded by sore throat (non-haemolytic streptococci isolated after admission). Previous history of frequent sore throats. Heart showed mitral incompetence on admission. Given one routine course of serum; six days later rash developed and lasted three days. Afebrile five days after serum. Allowed up thirty-nine days after serum. Six months later heart unchanged, and no further evidence of rheumatism.

7. Female, aged 49. Acute rheumatic polyarthrititis, duration two weeks, with no precedent sore throat. Previous acute rheumatism as a child; mitral incompetence on admission. Given one routine course of serum. No rash. Afebrile fifteen days after serum, and allowed up thirty days after. Heart on discharge as on admission.

8. Female, aged 14. Acute rheumatic polyarthritis, duration thirteen days, preceded by growing pains. Heart showed evidence of mitral disease on admission. Given one routine course of serum. Rash developed three days after serum and persisted for four days. Considerable exacerbation of joint pains during rash. Afebrile ten days after serum. Allowed up eighteen days after serum. Heart as on admission when discharged.

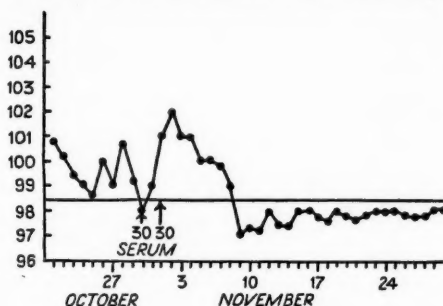


FIG. 3, Case 8.

9. Male, aged 34. Acute rheumatic polyarthritis, duration two weeks, with precedent sore throat (haemolytic streptococci isolated on admission). No previous rheumatism. Heart normal on admission. Given one routine course of serum. Rash developed eight days after serum, and persisted for three days. Afebrile four days after serum.

10. Female, aged 34. Acute rheumatic polyarthritis and erythema nodosum. Duration five days, with precedent sore throat (non-haemolytic streptococci isolated on admission). No previous rheumatic manifestation. Heart-sounds apparently normal on admission, but marked malar flush and cyanosis of lips. Moro's test positive, but no parenchymal lung shadows or other evidence of tuberculosis. Given one routine course of serum. Rash appeared three days later and lasted two days. Afebrile eight days after serum; allowed up nineteen days after serum. No further erythema after serum. Heart reported normal on discharge, but findings as on admission. Reported nine months later with definite evidence of mitral stenosis.

B. Acute cases, duration over three weeks.

11. Female, aged 30. Rheumatic polyarthritis, duration 2½ months, with recurrent fever. Admitted with mitral stenosis and incompetence. Given one routine course of serum. Rash, duration three days, with exacerbation of fever, appeared seven days after serum. Afebrile twenty days after serum; allowed up twenty-five days after serum.

12. Male, aged 36. Rheumatic polyarthritis, duration one month, preceded by sore throat. Previous attack of rheumatic fever, but no evidence of cardiac damage on admission. Given one routine course of serum. Afebrile fifteen days after serum, and allowed up thirty days after serum. Heart apparently undamaged on discharge.

13. Male, aged 27. Rheumatic polyarthritis, duration one month, commencing with sore throat (non-haemolytic streptococci isolated). No previous rheumatism and heart undamaged on admission. Given one routine course of serum. Rash developed six days after serum, and there

was exacerbation of fever during its three days of duration. Afebrile eleven days after serum. Allowed up twenty-three days after serum. Discharged with no evidence of cardiac damage. Reported ten months later with normal heart. No further evidence of rheumatism.

Thirteen cases of rheumatic polyarthritis treated by serum and without salicylate therapy are recorded. In these cases no relapses occurred.

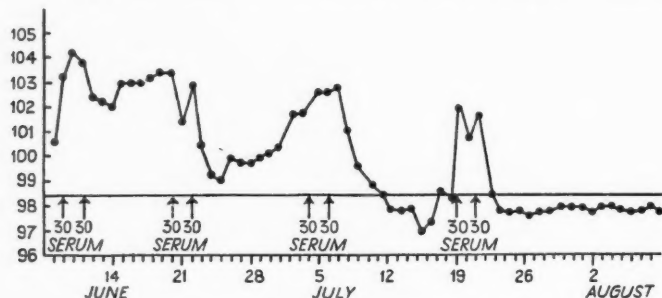


FIG. 4, Case 15.

C. Cases receiving serum in a different manner.

14. Male, aged 20. *Experimental method of administration.* Case of acute rheumatic polyarthritis, duration four days, with no previous sore throat. Admitted with evidence of organic cardiac damage; rheumatic nodules present. Serum given at 24-hour intervals in doses 10, 12, 15, 20, 25, 25, 30 c.c. (137 c.c.) Afebrile twelve days after first dose of serum. No rash. Discharged with heart as on admission. Reported sixteen months later with no change.

15. Female, aged 16. *One routine course of serum fails to control: repeated doses necessary.* Case of acute rheumatic polyarthritis, duration two weeks, preceded by sore throat (haemolytic streptococci cultured after admission). Previous attack of acute rheumatism in childhood. On admission considerable cardiac enlargement present, but heart-sounds closed and of normal intensity. Given one routine course of serum. Not afebrile ten days later, and another course given by desensitizing method. Fever moderated, but never became completely normal. Further course given another thirteen days later, seven days after which patient became afebrile for the first time. Occasional slight evening temperature led to administration of a further course to which there was a mild febrile reaction lasting four days. Rashes of short duration followed third and fourth courses of serum. Allowed up ten days after last course of serum and discharged completely well in short time. Reported twenty months later completely fit and with no evidence of cardiac damage.

16. Female, 38. *One routine course of serum fails to control: repeated courses necessary.* Case of subacute rheumatic polyarthritis, duration of ten months, during which there were recurrent bouts of pain and fever. From time to time salicylates had been given, but never intensively. Had suffered previously from acute rheumatism. On admission evidence of mitral incompetence present. Admitted with fever (100°-101° F.) and flitting pains in joints. Given one routine course of serum and, as neither pains nor fever were abating, given another course fourteen days later. Rash marked after each

course. Became afebrile after second course, but recurrence of slight evening temperatures made another course necessary. Afebrile five days after this course. Later given course of T.A.B. protein shock for persistent pain in shoulder. On discharge showed mitral lesion as on admission. Nine months later there was no further rheumatic manifestation.

17. Female, aged 26. *Regarded as too ill for usual method.* Admitted for paroxysmal tachycardia. Previous attacks of acute rheumatism had left mitral incompetence and stenosis. While in ward developed acute sore throat (*Streptococcus viridans* isolated) and four weeks later joint pains and fever appeared. Serum given after one week's fever in doses at 24-hour intervals of 5, 7.5, 10, 15, 20, 25, 30 c.c. (112.5 c.c.). No rash appeared. Afebrile twenty-one days after last dose of serum. Uninterrupted recovery, with no further joint pains and no further tachycardia. Discharged three weeks after becoming afebrile, and reported eighteen months later with no further cardiac or joint manifestations, but heart murmurs unaltered.

18. Female, aged 21. *Experimental method fails to control: further course necessary.* Acute rheumatic polyarthritis, duration eight days, preceded by sore throat (haemolytic streptococci isolated). Previous attacks of acute rheumatism, frequent sore throats, with mitral stenosis on admission. Given serum in six doses of 10 c.c. at 24-hour intervals. Rash appeared nine days after first dose and lasted three days. Not afebrile fifteen days later, and one routine course of serum given by desensitizing method. Afebrile six days later; recovery uninterrupted: no further rash, and discharged thirty-four days after second course. Heart as on admission.

Five cases are presented in which no salicylate therapy was employed and serum was administered in a manner other than the routine method of dosage. In three of these it was necessary to give repeated courses as a single course of serum failed to control the pain and fever. Of the other two, one was so ill with carditis that it was deemed wise to give serum in repeated small doses.

2. Cases which had Salicylates Before Serum

A. Acute cases of duration less than three weeks.

19. Male, aged 36. *Salicylates before admission, amount probably sub-effective.* Acute rheumatic polyarthritis, duration twelve days, with preceding sore throat (haemolytic streptococci cultured on admission). Growing pains as child, but heart normal on admission. Given unknown amount salicylate previous to admission. Fever on admission 101°-102° F. One routine course of serum given. Suffered general slight pruritus but no rash. Afebrile twelve days after serum. Up twenty-five days after serum. No evidence of cardiac damage seventeen months later.

20. Male, aged 30. *Salicylates before admission, probably subeffective dosage.* Acute rheumatic polyarthritis, duration seven days. No previous sore throat (haemolytic streptococci cultured on admission). Previously suffered acute rheumatism, but heart apparently undamaged. Unknown quantity of salicylates given for five days before admission. Temperature on admission 101°-102° F. Given one routine course of serum. Rash

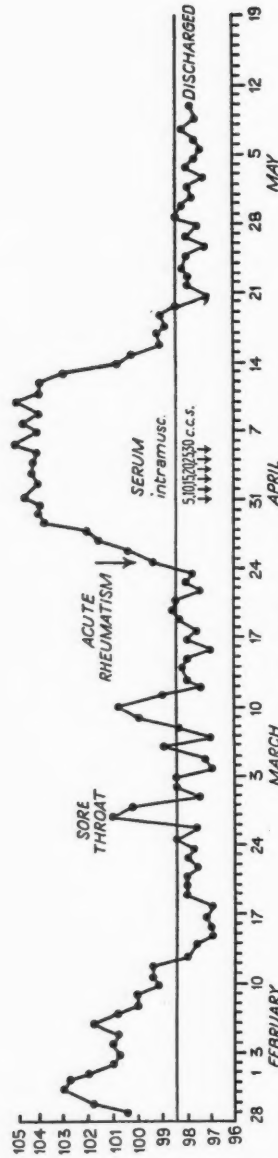


FIG. 5, Case 17. Daily maximum temperature.

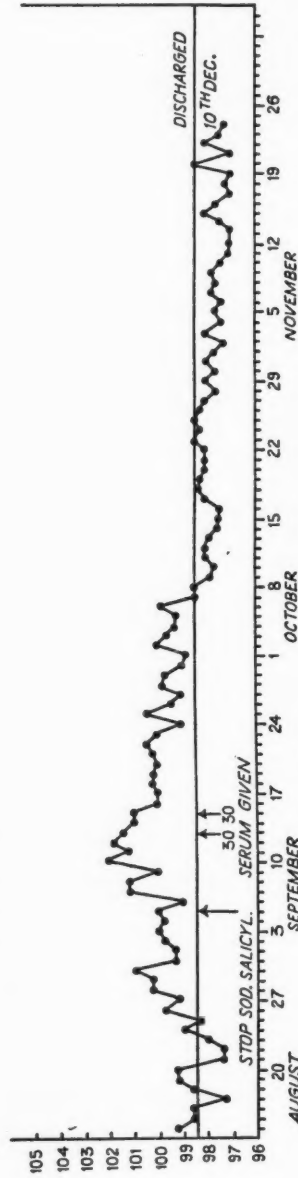


FIG. 6, Case 26. Daily maximum temperature.

developed four days after serum, lasting two days. Afebrile nine days after serum. Up twenty-three days after serum.

21. Female, aged 41. *Salicylates given previous to admission, probably in subeffective amount.* Acute rheumatic polyarthritis, duration two weeks. No sore throat (*Streptococcus viridans* obtained on admission). Growing pains as a child. Admitted with mitral stenosis. Given unknown amount of salicylates previous to admission. Admitted with temperature 100°-101° F. Given one routine course of serum. Rash appeared six days after serum and lasted three days. Afebrile eleven days after serum. Allowed up thirty-six days after serum.

22. Female, aged 25. *Relapsed after salicylates.* Acute rheumatic polyarthritis, duration ten days, with precedent sore throat. Admitted with normal heart findings. Fever on admission 101°-102° F. Given sodium salicylate 120 gr. daily for sixteen days. Afebrile on seventh day of salicylates, but relapse of pain and fever immediately on stopping salicylates on sixteenth day. Given one routine course of serum two days later. Rash developed eight days after serum and lasted three days. Afebrile seven days after serum. Up twenty days after serum. Discharged with apparently normal heart.

23. Male, aged 46. *Uncontrolled by salicylates; probable cause subeffective dosage.* Acute rheumatic polyarthritis, duration fourteen days, no precedent sore throat. No previous history of rheumatism. Admitted with weak heart-sounds, foetal rhythm, and cyanosis. Temperature 100°-101° F. on admission. Given salicylates averaging 83 gr. daily for twenty days. Still febrile (temperature 100°-102° F.) at the end of that period, so given one routine course of serum. No rash. Afebrile ten days after serum. Allowed up thirty-four days after serum. Pleurisy and phlebitis of femoral veins developed on thirteenth and fourteenth days of salicylate therapy. Seen twenty months later, cardiac rhythm still tic-tac, but not breathless, and no further trouble from rheumatism.

24. Female, aged 17. *Subeffective salicylates given for short period after admission.* Acute rheumatic polyarthritis, duration seven days. Had previously suffered acute rheumatism and chorea. Admitted with mitral stenosis and incompetence. Temperature 102°-103° F. Salicylates given for three days, but stopped. Pericardial rub appeared day after admission. Given one routine course of serum on stopping salicylates. Transient rash seven days after serum. Afebrile nineteen days after serum. Pericardial friction disappeared twenty-eight days after admission. Tachycardia (100-110 per min.) persisted for weeks. Has since been in ward twice with cardiac failure, but no arthritis or chorea in four years following the treatment by serum.

25. Male, aged 16. *Relapse after salicylates.* Acute rheumatic polyarthritis, duration three weeks. No previous rheumatic fever, but had suffered slight joint pains when aged 14. Heart showed mitral incompetence on admission. Fever 102°-103° F. on admission. Given sodium salicylate averaging 55 gr. daily (120 gr. daily for first four days) over twenty-four days. Relapsed thirty-five days after admission. After three days of pain and fever (temperature 101°-102° F.) was given one routine course of serum. Rash, duration three days, appeared seven days after serum. Afebrile twelve days after serum, and discharged twenty-seven days after serum.

B. Acute cases of duration more than three weeks.

26. Female, aged 36. *Salicylates failed to control.* Case of subacute rheumatic fever, duration ten months. Had suffered from previous attacks of acute rheumatism. Admitted with mitral stenosis. Temperature 99°-100°-101° F. on admission. Given salicylates averaging 90 gr. daily over twenty-one days. Fever still 100°-101° F. Given one routine course of serum. No rash. Afebrile twenty-three days later, but not allowed up for eighty days owing to cardiac condition. (Digitalis was given.)

27. Female, aged 20. *Given two days salicylates (subeffective) after admission.* Case of subacute rheumatic polyarthritis, duration nine weeks. Had recurrent sore throats during this nine weeks. Previously suffered many sore throats, and was admitted with mitral stenosis. Afebrile after admission till tonsillitis occurred, after which some slight nocturnal fever (99°) and marked flitting joint pains. Given salicylates for two days, and then one routine course of serum. Slight febrile reaction immediately on giving serum. Afebrile on third day. Rash appeared on seventh day and lasted three days. On eighth day patient suddenly collapsed with alarming dyspnoea and tachycardia. There was slight fever. Remained severely ill with these symptoms for two days; thereafter recovery was uninterrupted, but patient was kept in bed for a long time on account of her cardiac condition.

28. Male, aged 36. *Subeffective salicylates before admission.* Case of subacute rheumatic polyarthritis, duration seven weeks, preceded by sore throat (haemolytic streptococci cultured on admission). No previous rheumatic history, but heart showed mitral incompetence on admission. Fever on admission 100°-102° F. Given one routine course of serum. Rash three days later, duration one day. Afebrile ten days after serum, but there was later fever owing to staphylococcal boil on buttock. Allowed up thirty-three days after serum.

29. Female, aged 37. *Failure to respond to salicylates.* Case of subacute rheumatic polyarthritis, duration five months, commencing with sore throat. No previous rheumatic manifestations, and heart normal on admission. Given sodium salicylate averaging 120 gr. daily for three months previous to admission. Temperature on admission 99°-100° F. Given one routine course of serum. Rash seven days later, duration three days. Temperature exacerbated during rash, but then fell sharply to normal. Afebrile ten days after serum. Up thirty-three days after serum. Discharged with normal heart findings, and heart normal thirteen months later.

30. Female, aged 13. *Unknown quantity of salicylates (probably subeffective) given before admission.* Case of subacute rheumatic polyarthritis, duration seven weeks; preceded by sore throat. Previously suffered from acute rheumatism, and admitted with embryocardia and paroxysmal tachycardia. Temperature on admission rising to 99° F. at night. Given one routine course of serum. Rash, lasting three days, developed eight days after serum. Afebrile eleven days after serum (i.e. on fading of rash), and no further nocturnal fever. Tonsillitis (haemolytic streptococci obtained) developed five weeks after serum treatment, but no further joint pains. Paroxysmal tachycardia frequent till discharge after thirteen weeks in hospital.

C. Cases receiving serum in a different manner or dosage.

31. Male, aged 47. *Manner of dosage unusual—treated by another physician.*

Given unknown quantity of salicylates before admission. Case of acute rheumatic polyarthritis, duration three weeks. Three previous attacks of acute rheumatism. Admitted with mitral stenosis. Admitted with fever 99°–100° F. Given serum in doses of 30 cc. 1, 11, and 14 days after admission. Afebrile three days after last dose. Slight rash after first dose. Allowed up thirty-five days after admission. Heart normal on discharge.

32. Female, aged 22. *One course of serum fails to control. Given unknown (probably subeffective) quantity of salicylates before admission.* Case of acute rheumatic polyarthritis, duration six weeks, preceded by sore throat (haemolytic streptococcus obtained on admission). Previous acute rheumatism; mitral stenosis observed on admission. Temperature on admission 101°–102° F. Given one routine course of serum. Not afebrile twelve days later. Serum repeated (desensitizing method). Afebrile three days after second course, but slight recurrence of pain and fever led to further course eight days after second course. Immediate exacerbation of fever on giving serum, afebrile in five days; allowed up ten days after last course and soon discharged. Seen four months later in very good health.

33. Male, aged about 40 years, a medical man. *Uncontrolled by salicylates.* Case of subacute rheumatic polyarthritis. Suffered slight previous acute rheumatism leading to mitral incompetence; but led a very active healthy life. In this attack was given 60–90 gr. of sodium salicylate daily intermittently over five weeks. Patient then refused to continue with salicylates as he vomited after every dose. At this time his fever was 99°–100° F., and he was severely ill with pain and exhaustion. Owing to severity of his illness, he was given 10 c.c. of serum daily for six days (60 c.c.). Rash, duration four days, came eleven days after the first dose. Afebrile ten days after first dose, and discharged thirty-two days after first dose. Four months later was playing golf again, and was exceedingly grateful for serum.

34. Male, aged 49. *Uncontrolled by salicylates. Given serum in divided doses as severely ill on admission.* Case of subacute rheumatic polyarthritis, duration 4½ months. Previous attacks of rheumatic fever, and admitted with mitral stenosis. Given large quantities of salicylates (exact amount unknown) before admission. Temperature on admission 100° F., and patient was exceedingly thin and wasted. Given serum in doses daily of 5, 7·5, 10, 15, 20, 25, 30, 35 c.c. (147·5 c.c.). Rash, duration three days, nine days after first dose. Slight exacerbation of fever during rash. Afebrile eleven days after first dose of serum, but no pain after fourth day. Allowed up forty days after serum. Is very well, quite fat, and no further rheumatic manifestation, fourteen months later.

35. Female, aged 26. *Given unknown quantity of salicylates before admission. Relapsed after serum and required further course.* Subacute rheumatic polyarthritis, duration seven months. Had suffered previous rheumatic fever. Admitted with evidence of cardiac damage, and with fever of 100°–101° F. Given one routine course serum. Rash, duration two days, nine days after serum. Afebrile on tenth day after serum. Allowed up twenty-one days after serum, and discharged twenty-eight days after serum. Relapsed ten days later, and re-admitted for successful treatment by further course of serum. (Discharged five weeks after.)

3. Cases Given Salicylates After Serum.

36 and 37. Female, aged 29, and female, aged 19, are not reported in detail. Both cases were given salicylates so soon after serum that the effect of serum

was masked by that of salicylates. These cases were the second and third treated in the series. Case 36 has since suffered a relapse of subacute rheumatic polyarthritis.

38. Female, aged 49. Acute rheumatic polyarthritis, duration two weeks. (Haemolytic streptococci cultured on admission, from throat.) Previous attack of rheumatism left mitral stenosis, present on admission. Temperature on admission 100°–102° F. Serum, one routine course, given third day after admission; rash developed on eighth day after serum, and afebrile on tenth day. Slight evening fever persisted, and rheumatism relapsed twenty-four days after serum. Salicylates, 120 gr. daily brought about uneventful recovery. No change or relapse 2½ years later.

(N.B. This case would now receive a further course of serum.)

39. Female, aged 37. Acute rheumatic polyarthritis, duration eight days, preceded by sore throat. Previous attacks of acute rheumatism. Admitted with mitral stenosis and embryocardia. Given one routine course of serum. Rash, duration two days, on fifth day after serum. General temperature lowered, but never afebrile. Salicylates, 180 gr. daily given twenty-five days after serum, and temperature normal next day. Reported two years later—is very well, no further change in heart and no further rheumatism.

40. Male, aged 21. Acute rheumatic polyarthritis, duration five days, preceded by sore throat. No previous rheumatism, and heart normal on admission. Given one routine course of serum. Rash (transient) six days later. Nine days after serum complained of pain in chest, and eleven days after had first a pleural, then pericardial, friction. Joint pains reappeared and fever exacerbated. Sixteen days after serum was given salicylates 120 gr. daily, increased to 180 gr. daily. Afebrile after seventeen days of salicylates. Reports a year later with definite mitral stenosis.

41. Male, aged 20. Case of acute rheumatic polyarthritis, duration six weeks, with no precedent sore throat. Previous attack of acute rheumatism, and admitted with evidence of cardiac damage. Given one routine course of serum, and pain free and afebrile ten days later. Transferred to convalescent home for prolonged bed convalescence, and immediately relapsed. Relapse controlled by salicylates. (This case was treated outside our charge.)

These six cases in which recourse was had to salicylates after serum therapy were early members of this series. In similar cases recorded above, occurring later in the series, serum has been employed in second and third courses when the first has failed to control pain and fever.

Three Patients Who have Died

Of the sixty or so cases of various conditions, rheumatic and otherwise, which have been treated with antiscarlatinal serum, three have died. These cases are reported below. It may be noted that there is one case in which explanation of the cause of death is doubtful; one died from heart failure due to adhesive pericarditis, and the third from intracranial tumour.

42. Male, aged 17. *Rheumatic arthritis with severe pancarditis. Death from cardiac failure.* Had suffered no previous rheumatism. Had been ill for six weeks before admission with fever 102°–103° F., tachycardia and

dyspnoea, and mild joint pains of flitting nature. Given large quantities of salicylates before admission. On admission temperature 100° – 101° F. Heart grossly enlarged, with aortic regurgitant murmur and double mitral murmur. Venous pulsation present in neck. Red blood cells 3,400,000. Haemoglobin 70 per cent. (later it fell to 50 per cent.). Seven days after admission was given intramuscularly 5, 7.5, 17, and 30 c.c. of serum at 24-hour intervals. There was some remission of fever, but as he was still febrile he was given one routine course (desensitizing method) of serum thirteen days after the first course. This had no effect on fever. After two further courses he became afebrile, joint pains ceasing and tachycardia abating. Pallor and dyspnoea were still severe. At this stage he was judged well enough to transfer to a convalescent home for a prolonged stay, but relapsed one week later. Readmitted to Royal Infirmary, Edinburgh, with high fever, tachycardia, cyanosis, and dyspnoea, with slight joint pains. Signs of adherent pericardium developed. Died three weeks after re-admission. Carditis was so severe that blood cultures were repeatedly taken, endocarditis lenta being suspected.

P.M. Report: Peritoneal cavity is distended with fluid; there is fluid also in the pleural sacs. Pericardial sac completely obliterated by firm fibrous adhesions. The heart was greatly enlarged, myocardium being hypertrophied, pale in colour, and of very soft consistence. Mitral and aortic valves showed firm hard warty vegetations characteristic of rheumatic endocarditis.

This case was rather unusual in displaying so progressive and rapid a pancarditis with no previous history of any form of rheumatism. Joint pains were never very marked, and the joints were at no time red or swollen.

43. Male, aged 50. *Rheumatic polyarthritis, died with intracranial tumour.* Had suffered pain and fever for five days, and on admission showed pericarditis. Given one routine course of serum. After serum became mentally confused and stuporose. Died in coma without localizing signs two months after admission.

P.M. Report: Acute rheumatic endocarditis on mitral, tricuspid, and aortic valves, superimposed on chronic rheumatic lesions. Chronic adhesive pericarditis present. Astrocytoma of ependymal origin (Dr. J. H. Biggart) in floor of fourth cerebral ventricle, giving rise to slight internal hydrocephalus.

The rheumatic condition in this case was not associated with the cause of death.

44. Female, aged 22. *Acute rheumatic fever with necrotizing arteritis (periarteritis nodosa).* History of previous rheumatic fever. Had suffered from fever and pains for two weeks before admission. Pains described as being in legs and arms rather than in joints. Admitted with fever of 103° – 104° F., and evidence of cardiac damage. One routine course of serum given. Marked remission of fever on fifth day after, but on sixth day with appearance of rash there was exacerbation of fever and of pains, lasting for five days, its disappearance coinciding with the fading of the rash. Fourteen days later (i.e. twenty-seven days after first dose of serum) there was a reappearance of pains and fever, with steadily increasing pulse-rate. 30 c.c. (half a course) of serum was given (desensitizing method) to which there was no immediate abnormal reaction, and temperature fell on the third day after

serum. Temperature and pulse frequency were normal for two days, and patient was looking and feeling very well. In the afternoon temperature rose suddenly to 104° F., and patient sank into coma and died.

P.M. Report: Pleural, peritoneal, and pericardial sacs were healthy. Respiratory system and brain and alimentary system normal macro- and microscopically. Myocardium was normal except for some softness; endocardium and pericardium quite healthy. Small multiple nodular lesions were seen on the smaller branches of coronary vessels. These were also discovered in pancreas and in kidney in relation to vessels. On microscopic section these proved to consist of a necrotic core centred in the wall of the vessel, with a zone of surrounding cellular infiltration in which the principal cell was the small lymphocyte. *B. coli* of mucoid, haemolytic variety were recovered from the sphenoidal sinus and from the cerebrospinal fluid (in which they were almost certainly a post-mortem contaminant).

It is difficult to assess the cause of death in this case. The first thing that is clear is that death, delayed five days after the injection, could not have been anaphylactic. Tissue allergy might develop at such an interval. It seems likely that death is to be related to the necrotizing arteritis. The problem in this case is whether the lesions are to be related to the injections of serum or whether serum can be exonerated from any responsibility for death. It has been suggested that repeated doses of serum may cause such lesions in experimental animals. However, there is an increasing mass of evidence that periarteritis nodosa or a necrotizing arteritis may be met with in association with acute rheumatic fever in which there has been no suggestion of any treatment which might give rise to allergic phenomena. Friedberg and Gross (43) in the past two years have met with eight cases of typical periarteritis nodosa, four of which had conclusive evidence of rheumatic heart disease at necropsy. Cases have also been recorded by Rothstein and Welt (44) (Aschoff bodies in the heart with periarteritis in coronary and other vessels) and by Neale and Whitfield (45) (chorea rheumatica with periarteritis). Herlitz has reviewed a number of cases of periarteritis nodosa and concludes that they may be associated with a variety of streptococcal lesions, among them acute rheumatism. Other cases where this association has been present have been presented by Benda (46), by Löwenburg (47), by Jänssen (48), and by Lamb (49). Experimental attempts to induce rheumatism in animals have resulted in lesions resembling both acute rheumatism and periarteritis nodosa (Siegmund (50), Klinge (51), Metz (52)). We feel that case 44 represents an association of this type, and we suggest there is no evidence that serum was in any way responsible for the death.

Untoward Results of Serum Administration

From the first the principal fear in using serum in acute rheumatism was that the introduction of so much foreign protein to the body during a disease

widely believed to be allergic in nature would lead to disastrous reactions. Warnings to this effect have appeared in the literature. Schlesinger (53) remarks, 'In my experience there are great dangers in this form of therapy in acute rheumatic subjects, and those who propose to try it should be warned to expect occasional very severe reactions, even leading to a fatal collapse'. Hitchcock, McEwan, and Swift (54) refer to two cases in which severe anaphylactoid manifestations followed the use of concentrated antisera, while Small (55) in his series of cases treated with a concentrated antiserum experienced disturbing cardiac manifestations after serum which he termed focal reactions. Our experience leads us to believe that the unpleasant reactions of serum therapy are sufficient to warrant such treatment being carried out only in hospital, or under equivalent conditions in private practice; but we believe also that the dangers of such therapy can be easily exaggerated.

The following represent the principal untoward results of concentrated antiscarlatinal serum administered to some sixty cases, over forty of which have been cases of acute rheumatic polyarthritis. First, there is a certain amount of local pain in the buttock as the result of the intramuscular introduction of 30 c.c. of material. Secondly, in the great majority of cases, immediately upon injection there is some exacerbation of temperature, which may persist for any time up to the fading of the rash. This fever is not accompanied by the gross sweats that characterize acute rheumatism under salicylate therapy. Thirdly, about 75 per cent. of all cases develop a serum rash. This usually takes the form of patchy erythema or an itching urticaria, which appears between the third and ninth day (average fifth to sixth day) after the first injection of serum, and which lasts for a few hours to three days. We have not met with the severer form of serum sickness characterized by oedema of the eyelids or oedema glottidis. In a large proportion of cases during the rash there is exacerbation of temperature, not infrequently combined with some increase in, or reappearance of, joint pains. With the fading of the rash pains and fever disappear and the patient proceeds to convalescence. There is no association between the presence or absence of the rash and the eventual recovery, as patients who show no rash recover satisfactorily.

One serious reaction ascribed to serum was experienced in Case 27. In this case, a patient with definite evidence of carditis (mitral stenosis), on the eighth day after serum, and the day after the appearance of a rash, an alarming collapse with dyspnoea, cyanosis, and tachycardia was observed. Presumably this is the type of reaction which Small (55) might have termed a 'focal' reaction. This is the only case in which a reaction ascribable to serum has occasioned serious alarm. Hitchcock, McEwan, and Swift (54) describe a similar case. Since then serum has been given to many cases with evidence of active carditis, but if the cardiac condition is extremely advanced it is preferable to give gradually increasing daily doses in place of the two ordinary doses in the course (e.g. Cases 33, 17, 34).

The Results of Serum Therapy

Hitchcock, McEwan, and Swift (54) draw attention to the difficulties in assessing the value of serum therapy: 'The evaluation of the effect upon rheumatic fever of any therapeutic measure is a matter of no mean difficulty. The universal application of salicylate therapy has served to mask the tremendous variability in the course of the disease, particularly with regard to such aspects as the arthritis and fever . . . it has been no unusual experience with us to observe marked improvement in these manifestations, occasionally even complete relief, under expectant therapy alone, along with a few days of hospitalisation.' In order to overcome this latter possibility these authors insisted on a control period of a week in hospital without treatment. We have not felt justified in keeping patients so long untreated, the majority of our cases receiving serum after forty-eight hours in hospital. Small has asserted that cases must be watched for at least three weeks after treatment before assertions of successful treatment can be made. Nearly all our cases have had such an observation period.

In assessing the value of any form of therapy we feel there are five points on which the inquirer will particularly wish for information. 1. The duration of pain and fever. 2. The relapse rate. 3. The average duration of confinement to bed and to hospital. 4. The course of convalescence. 5. The incidence of sequelae.

1. *The duration of pain and fever.* For the purpose of this consideration any temperature over 98.4°F . is accepted as fever. It must be pointed out that the natural concomitant of giving serum is a febrile reaction, partly protein shock (immediate fever) and partly allergic in nature (serum sickness), and not till the rash has faded will a patient become afebrile. Thus the figures for duration of fever after serum therapy tend to be those which we would expect from a massive course of serum rather than those due to the rheumatic process itself. But for the sake of comparison with salicylates a graph is appended with curves showing recoveries with serum, with salicylates (Lyon's series), and untreated (Hood (67) and Graef, Parent, Zitron, Wyckoff (68)) cases respectively. It will be seen (Fig. 7) that the serum therapy gives a smaller proportion of cases afebrile within the first five days than in Hood's cases—the fever of serum disease being responsible—but that after fifteen days nearly 40 per cent. of Hood's and 68 per cent. of the New York untreated cases were still febrile, whereas serum-treated cases show only 10 per cent. still febrile. After twenty days there were 13 per cent. untreated cases afebrile, whereas all serum-treated cases were afebrile. There can be no doubt from these curves that serum is an effective therapy, but so far as fever is concerned salicylates will more quickly return the patient to normal than will serum.

2. *The relapse rate.* Excluding the cases in which death occurred, there were four cases of true relapses following one course of serum, i.e. cases becoming afebrile to be followed at varying intervals by a rise in temperature and recurrence of joint pains. Two of these relapsed in hospital (Cases 38 and 40), and were given salicylate of soda. Two relapsed after discharge

(Case 35 being readmitted for serum, Case 41 being given salicylate of soda in a convalescent hospital). This represents a relapse rate of 10 per cent.

In addition to these there were five cases which did not become afebrile following a first course. In four of these further courses were given as follows: Case 15, three additional; Case 18, one; Case 32, two; and Case 16,

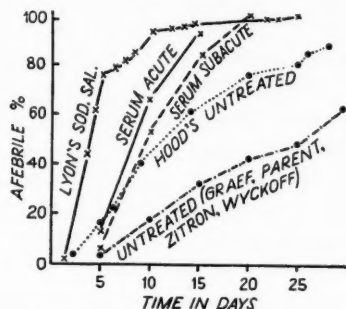


FIG. 7. The duration of fever in Lyon's salicylate-treated cases and in two series of untreated cases is compared with the duration in serum-treated cases which have less than three weeks' history (acute) and more than three weeks' history of fever (labelled subacute in the graph).

three additional. Progressive improvement followed each course, and the temperature eventually became normal, without recurrence of rheumatic manifestations. One case, 39, following one course of serum, was given salicylate of soda when the temperature did not fall to normal.

If the five cases whose condition did not become afebrile, following one course of serum but did so following further courses be considered relapses, then the relapse rate is 23 per cent. (nine out of forty). This compares favourably with the relapse rate of thirty-eight patients, showing fifty-eight relapses in Lyon's (23) series of 100 cases. It would appear, however, that these five cases were treated with an inadequate amount of serum and cannot be regarded as true relapse cases but rather as resistant to 60 c.c. of serum.

The rate of 23 per cent. approximately represents the proportion of cases in which more than one course of serum may be necessary.

3. *The average duration of confinement to bed and to hospital.* No information could present a more fallacious source from which to derive the desirability of any form of therapy. Such times will be influenced by the personal habit of the physician, by the pressure on the beds in an institution, or even the desire to retain cases in hospital for purposes of demonstration. However, these figures are presented because they have habitually been given in such discussion, and not for their scientific value. Cases which died and cases which were retained in bed and hospital on account of cardiac conditions (paroxysmal tachycardia, Cases 17 and 30) have not been included in the computations.

Average period of stay in hospital (37 cases)	42 days.
Average period in bed after first dose of serum	29 days.

4. *The course of convalescence.* In assessing this it is impossible in this series to convey more than impressions. We believe that the convalescence once the rash has disappeared is much more rapid than with salicylates. In particular, besides the much lower incidence of relapses, there is no salicylate sweating, and there is less anaemia and debility. The general opinion of a wide range of physicians is the only method by which such impressions might be checked.

5. *The incidence of sequelae.* We have no intention of reaching any conclusion from this short series. It is published in the hope that a large series suitable for comparison with salicylates may become available over a period of years. The difficulty is in obtaining adult cases of acute rheumatism in which the heart is not already damaged. Here we have thus far observed two cases, serum treated, in which there was evidence, after recovery, of mitral disease not previously known to be present.

Previous Attempts to Employ Sera in Acute Rheumatism

In 1902 Menzer (56) recorded the use of antistreptococcal sera prepared for him by Merck of Darmstadt against organisms which he recovered from the pharynx. He treated all types of rheumatism, including seven acute cases. Other German writers reported favourably on the use of Menzer's serum. Menzer (63) has since abandoned serum in favour of non-specific protein shock, and Hitchcock, McEwan, and Swift hold that this abandonment may be taken as valuable evidence of the uselessness of antistreptococcal sera. In 1927 Small (55) described an organism, the *Streptococcus cardio-arthritis*, a non-haemolytic streptococcus, and prepared a concentrated antiserum against this organism, for the use of which was claimed very striking therapeutic results in all forms of rheumatism (including carditis). The claims made for this serum have been examined by Hitchcock, McEwan, and Swift (54), by Wilson (57), and by Hill (58), who separately conclude its uselessness. Hitchcock, McEwan, and Swift employed a concentrated antiscarlatinal serum and were not impressed by its value. In their series they treated five cases of acute rheumatic polyarthritis with a concentrated antiscarlatinal serum prepared for them by the New York City and State Health Department. No statement is made as to the dose in units of antitoxin, the volume of serum (concentrated) given being 6, 10, 16, 23, and 55 c.c. in the various cases, no case coming up to the full 60 c.c. which we employ as a course.

There have been a number of reports of the treatment of single and small groups of cases, such isolated cases having very little value in determining the value of therapy in a disease like rheumatism. Thus Toogood (59) reports a case of rheumatic carditis with fever which became afebrile after three doses of 10 c.c. of concentrated antiscarlatinal serum (P. D. & Co.). Barach (60) reports a similar case of rheumatic endocarditis with fever in which lysis followed 10 c.c. of antiscarlatinal serum (lederle), there having

been extensive unsuccessful use of salicylates. Markson (61) records a case of erythema nodosum with tonsillitis, and endocarditis, 'resistant' to previous salicylate therapy, which reacted favourably to a polyvalent antistreptococcal serum. Coope and Pygott (62) have reported eight cases of acute rheumatism in which concentrated antiscarlatinal serum gave promising results.

More recently Coburn and Pauli (37) have reported discouragingly on the use of specific antisera. They used an antistreptococcal (haemolytic) serum prepared by the New York State Department of Health, polyvalent in that it was capable of neutralizing the toxins of about 70 per cent. of the organisms which they had determined to be effective in precipitating acute rheumatic manifestations in New York. They treated prophylactically with this antiserum patients known to be of rheumatic tendency who developed haemolytic streptococcal tonsillitis. The subjects were passively immunized with doses ranging from 40,000 to 100,000 Dick units (i.e. 1,800 new units). Of the passively immunized, four cases developed rheumatic recrudescences, despite the fact that the antiserum was completely capable of neutralizing the toxins produced by the haemolytic streptococci in the throats of these cases. Coburn and Pauli think that prophylactic serum may enhance the severity of a subsequent rheumatic attack. Although the dose employed by these workers was sufficient to render the patient strongly Dick negative, their maximum dose corresponds to only 1,800 'new units' of antitoxin. This represents one-tenth of the antitoxin content of our routine 'course' of serum, although it is not here maintained that this fact would explain Coburn and Pauli's poor results. It has been our own clinical experience that sore throats due to haemolytic streptococci may develop after large doses of antiscarlatinal serum.

The Element of Protein Shock

The evidence submitted in the foregoing cases shows that concentrated antiscarlatinal serum will terminate an attack of acute rheumatic polyarthritis. The question inevitably arises whether or not the success of this method depends on the element of protein shock involved in the introduction of some 12 grm. of horse pseudo-globulins into the body. There is some evidence that the body reacts to the foreign protein in the definite exacerbation of the fever which occurs in most patients immediately after the giving of serum. Petersen (65) has treated acute rheumatism by means of protein therapy and claims 40 per cent. complete success and 30 per cent. improvement in his cases. Menzer (63) also advocates protein therapy, and Miller (64) reported 80 cases out of 93 completely cured by means of from one to four injections of T.A.B. vaccine intravenously. He records that 'thirty of these cases had been under active salicylate therapy without benefit'. Hitchcock, McEwan, and Swift observed in the series treated by various concentrated antisera, to which reference has already been made above,

that very similar results were obtained whatever kind of concentrated anti-serum was employed, and remark that it seems unlikely that the specific antibody content has anything to do with the reaction of rheumatic fever to sera.

By the kindness of Parke Davis & Co. we have been able to test the effect of concentrated horse serum containing the same amount of protein, but no specific antibodies, on cases of acute rheumatism. As in giving a 'course' of serum, two injections intramuscularly of 30 c.c. each of concentrated horse serum was given to three cases of acute rheumatic polyarthritis. This involved a dose of about 12 grm. of pseudo-globulins; no albumin, globulin, or euglobulin.

45. *Control 1.* Male, aged 24. Case of acute rheumatic polyarthritis, duration one week, with no precedent sore throat (haemolytic streptococcus cultured on admission). Previous history of acute rheumatism; mitral stenosis on admission. After four days in ward (temperature 100°–102° F.) was given one course of non-specific serum (sensitive to horse serum and therefore given by the desensitizing method). Rash appeared on the day after first injection, and lasted two days. Slight increase in temperature (102°–103° F.) for first four days after injection. Fourteen days after serum pain and fever unabated, and similar to state on admission. Then given sodium salicylate 120 gr. daily for thirteen days, later increased to 180 gr. daily, after thirteen days of which he became afebrile.

46. *Control 2.* Female, aged 36. Case of acute rheumatic polyarthritis, duration two weeks. No precedent sore throat (haemolytic streptococci cultured on admission). Previous rheumatic fever; admitted with functional(?) mitral systolic murmur. Temperature 102°–103° F. Given one course of non-specific serum. No immediate reaction; rash on sixth day lasted four days, and afebrile eleven days after serum. Allowed up twenty-five days after serum, and immediately relapsed (temperature 99°–100° F., flitting joint pain and swelling). Given further course of non-specific serum, following which temperature exacerbated to 100°–102° F. Slight rash soon after second dose. Afebrile six days after serum. Rapid convalescence with no further relapse.

47. *Control 3.* Female, aged 44. Acute rheumatic polyarthritis, duration three weeks, not preceded by sore throat. Sore throats when young, but no other rheumatic manifestations. Temperature on admission 101°–102° F. Given one course of non-specific serum. Rash five days after serum (duration six days). Marked fever during rash, but on eleventh day rash, fever, and pain abated together. Afebrile for eight days, and then relapsed (temperature 103°). Further course of non-specific serum led to lysis four days after first dose of the course. Rapid convalescence.

The effect of serum in lowering fever is certainly not specific to anti-scarlatinal (or other antitoxic) sera. In so small a control series it is difficult to interpret the fact that all three cases showed at least one relapse each. A further control series will be necessary. It is possible that the protein injection is responsible for changing the rheumatic state, while the antibody content either lowers the virulence, or removes the precipitating cause, of that state; and for that reason non-specific sera show a high relapse rate.

Conclusions

1. Salicylate therapy has certain disadvantages and difficulties which have been discussed, the principal ones being a high relapse rate and the high incidence of cardiac sequelae; active search for a genuine antirheumatic agent is an urgent matter.

2. In a series of forty-four cases of acute rheumatic polyarthritis concentrated antiscarlatinal serum has proved itself an effective form of therapy worthy of extended trial.

3. As compared with salicylates serum therapy has disadvantages: (a) The average initial period of fever is somewhat longer. (b) There is a certain amount of discomfort owing to the resultant serum sickness, and the possibility of untoward reactions demands the careful precautions required in employing an experimental form of therapy which is not devoid of risk. While the incidence of unpleasant reactions is low, the possibility of a formidable reaction cannot be regarded as remote.

4. As compared with salicylates serum therapy has certain advantages: (a) A number of cases that are for one reason or another 'resistant' to salicylates (e.g. Cases 33, 34, 29) can be effectively treated with serum. (b) The incidence of relapses is considerably lower with serum than with salicylates, and in this series subsequent rheumatic recrudescences have been infrequent. (c) The length of stay in hospital and the duration and nature of convalescence compare very favourably with salicylates.

5. It is safe to give serum to very ill patients, even when suffering from grave carditis.

6. The immediate effects of serum are sufficiently satisfactory to justify its wider use with a view to determining its effect on the incidence of cardiac sequelae, which is the only part of the rheumatic syndrome dangerous to life.

7. It is unlikely that the effects of antiscarlatinal serum on acute rheumatic polyarthritis are entirely specific. Similar effects are reported here and elsewhere with non-specific protein therapy. A brief series of controls, showing a high relapse rate, indicate the possibility of combination of a non-specific element and a specific element in concentrated antiscarlatinal serum.

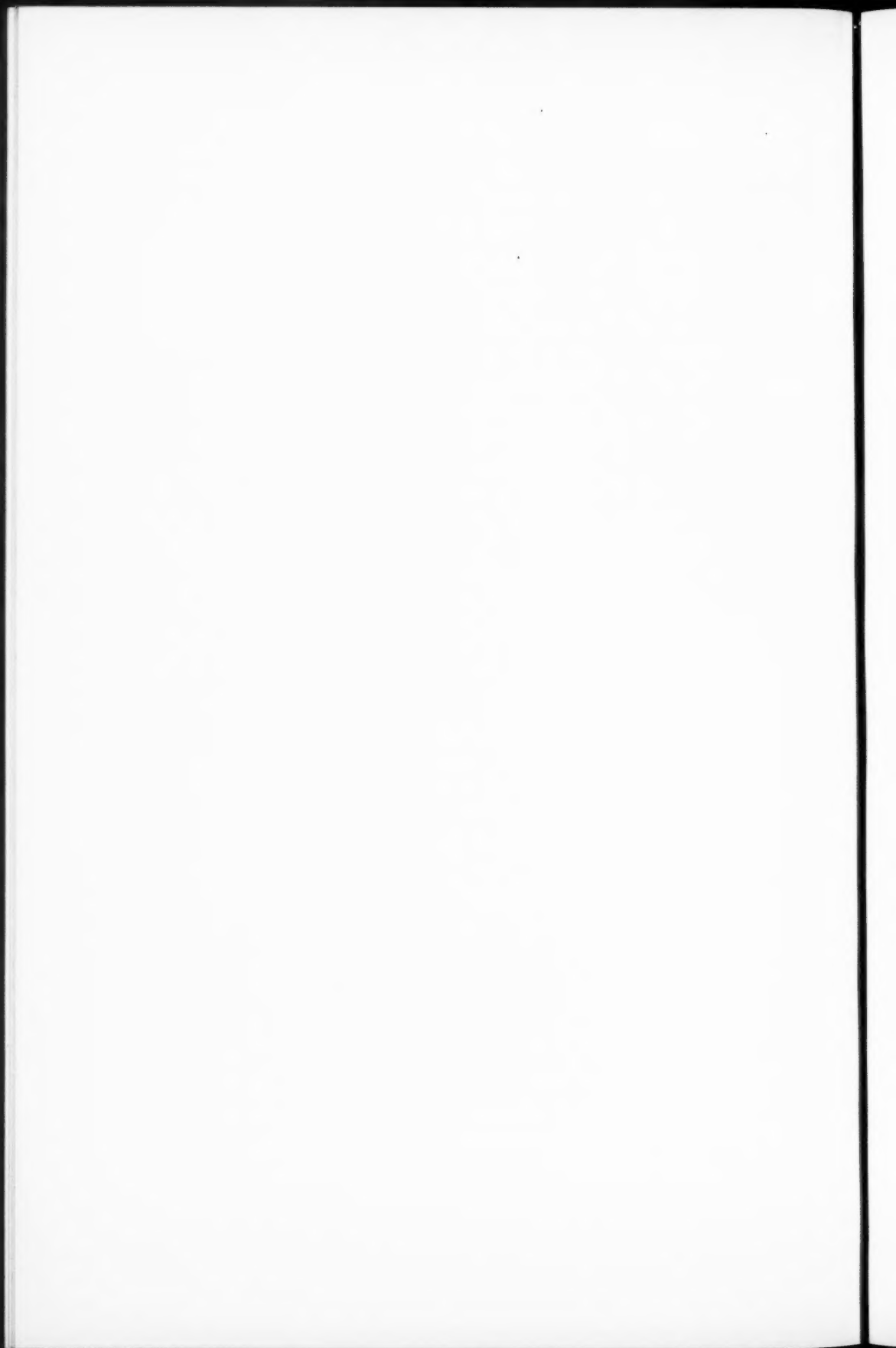
8. There is no evidence that either serum therapy, or the withholding of salicylates, was a contributory cause of death in the three fatal cases recorded in this series of forty-four treated with antiscarlatinal serum.

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THREE CASES OF IDIOPATHIC STEATORRHOEA (GEE-THAYSEN'S DISEASE)¹

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With Plate 4

Introduction

THE disease of which three new cases are reported in this paper was described first by Samuel Gee (12) (1888) under the term 'the coeliac affection' as characterized by light-coloured voluminous stools, emaciation, and meteorism, often accompanied by anaemia. Gee says: 'The coeliac disease is commonest in patients between one year and five years old: it often begins during the second year of life. Sometimes from India Englishmen return sick with the coeliac affection: seldom is it met with in adults who have never left England.'

Children present that variety of the disease which later is designated commonly as the coeliac affection, morbus coeliacus, coeliakie, Gee-Herter's disease, Herter-Heubner's disease, intestinal infantilism. The second group is made up of cases of tropical sprue. The third group is represented by cases of non-tropical sprue.

For a good many years the existence of non-tropical sprue was doubted. Subsequently, however, and chiefly through the observations and studies reported by Thaysen (29, 30, 31), it has been established that there occurs now and then a sprue-like disease in adults who give a past history of good health and have never been in the tropics.

Since the appearance of Thaysen's first paper on non-tropical sprue altogether seventy to eighty cases of this disease have been reported from various countries; in particular from Denmark: Thaysen (29, 31), Warburg and Jørgensen (33), Holst (17), and Geill (13); U.S.A.: Hanes and McBryde (15), and Germany: Hansen and v. Staa (16).

Thaysen succeeded in demonstrating that the three varieties present so many similar features that they have to be regarded as one disease, which he has designated as idiopathic steatorrhoea. His arguments in favour of this view were set forth in several papers published between 1922 and 1935; in particular his monograph 'Non-tropical Sprue' (29) (1932) and a paper of 1935 about ten cases of idiopathic steatorrhoea (31).

To-day the view advanced by Thaysen has been accepted, by Hansen and v. Staa (16) and by Hanes and McBryde (15), but as yet it has not been adopted generally in England, where it has been opposed, in particular

¹ Received October 26, 1936.

by Bennett, Hunter, and Vaughan (4) in a comprehensive paper covering fifteen cases of idiopathic steatorrhoea. The authors employ this term to signify 'adult coeliac disease' i.e. slowly developed—or late recognized—cases of the infantile coeliac disease, claiming that in most cases of non-tropical sprue the history of the affection may be traced back to childhood. The somewhat one-sided material from which Bennett, Hunter, and Vaughan have their experiences leads them not only to disagree with Thaysen in his parallelism of the three subdivisions of Gee's disease, but also to question the existence of the non-tropical sprue, or at any rate consider it an 'extremely rare occurrence'. In his last work Thaysen (31) has convincingly maintained his standpoint against this criticism.

The first of the cases to be mentioned here furnishes an additional and unquestionable confirmation of the point of view advanced by Thaysen.

Case Records

Case 1. Woman, aged 27, married. Family history negative. Past history of good health till the age of twenty; in particular, there was never any tendency to diarrhoea. The patient had never been in the tropics.

At the age of twenty she had had erythema nodosum, without sequelae. Between twenty-one and twenty-five there was a moderate degree of constipation but never diarrhoea.

The first admission to the Medical Department of the St. Elizabeth Hospital was 1-22 June 1935 (Reg. No. 282a/35), under the diagnosis of anaemia of pregnancy.

No previous pregnancy. Menses last present in October 1934. Nausea and vomiting from the second month of pregnancy, usually two to three times a day. In the last two to three months there had been increasing tiredness, palpitation of the heart, tinnitus, and several times attacks of weakness, approaching fainting spells; in the last days before admission, several small haematemeses. In March the haemoglobin percentage was 72. There had been no vaginal bleeding during the pregnancy. The bowels were said to have been a little sluggish, but the stools had been normal. She had been taking ordinary mixed diet, with plenty of vegetables and about 500 c.c. of milk daily.

Physical examination. Marked anaemia of the skin and mucous membranes. No jaundice. There was a conspicuous brownish pigmentation, with sharply defined borders, on the forehead extending out on the temples and down on the cheeks, also on the chin. No dermatitis. The papillae of the tongue were rather inconspicuous, but not truly atrophic. There were several aphthous patches on the tongue as well as in the sulcus alveolo-buccalis. No enlargement of peripheral lymph glands. Auscultation of the heart and lungs revealed no abnormalities. The uterus reached to 5 cm. below the xyphoid process. There was considerable oedema of the lower part of the legs.

Urine. No albumin or sugar. *Sedimentation test* (one hour): 130 mm.

Ewald test meal. Amount 75 + 20 c.c., well chymified; no mucus; Congo 19; phenolphthalein 46.

Faeces. No blood, mucus, or pus.

Blood examination. Hb.: 42 per cent.; red-blood count: 2,000,000; colour index: 1.05; volume percentage: 16; volume index: 0.86; white-blood count: 8,000; reticulocytes: 0.5 per cent.; platelets: 200,000; blood smear: moderate anisocytosis, no micro- or megalocytosis, no polychromasia, no abnormal forms. Differential count: neutrophils 70 per cent.; eosinophils 1 per cent.; lymphocytes 22 per cent.; monocytes 7 per cent. Price-Jones curve: mean diameter 7.323μ , σ 0.65μ , v 8.9 per cent.; microcytosis 0.8 per cent.; megalocytosis 0.8 per cent. Bleeding time: normal. Icterus index (Meulengracht): 6.

The patient was treated first with hepsol (4 c.c., intramuscularly daily), later with ferrum reductum (0.75 grm. thrice daily), but the anaemia became worse, and she was transferred to the Lying-in Department of the Rigshospital—with a view to the possible induction of premature delivery. Here she was treated with blood transfusion, which had a favourable effect, and with iron and liver extracts; under this treatment the haemoglobin percentage increased to 65. Labour took place at term, on 27 July, with normal spontaneous delivery. The patient was discharged from the hospital ten days later, feeling quite well.

At home she felt well for some time, but in the autumn she began again to be troubled with diarrhoea, which progressed to such an extent that finally she often had fifteen to twenty stools in twenty-four hours. The stools were very light in colour, thin and voluminous, unpleasant and frothy, amounting in weight up to 2 kg. per twenty-four hours. There were at the same time gnawing and oppressive sensations in the epigastrium, rumbling of the intestines, and flatulence. She noticed that the abdomen became distended and was 8–10 cm. greater in circumference in the evening than in the morning. She felt tired, nervous, and depressed, and she lost considerably in weight. She then remembered that even as early as the middle of pregnancy, before she became anaemic, there had been a brief period in which the stools had been light in colour and loose but not particularly voluminous. During her stay in the Lying-in Hospital she had noticed that the stools were voluminous and appeared fatty, but as she was given iron their colour was naturally dark.

These data suggested very strongly the possibility of idiopathic steatorrhoea, and the following examination, made in the St. Elizabeth Hospital, established this diagnosis unquestionably.

Second admission to this hospital, 4 November to 18 December 1935 (Reg. No. 428/35).

Physical examination. The patient was thin—in particular, the subcutaneous adipose tissue was very scanty—and looked tired. There was no anaemia or jaundice. The pigmentation of the face was a little less pronounced than on her first admission, but showed the same localization. There was a pronounced redness of tip and margins of the tongue; two days after the admission there was a new eruption of aphthous patches. Chvostek's and Trousseau's signs were negative. The abdomen was soft, giving everywhere a tympanitic percussion note. Circumference of the abdomen in the morning 72 cm., in the evening 83 cm.

Faeces very light in colour, oily, unpleasant and frothy, thin or mushy; up to five stools in twenty-four hours, making a total amount of up to 1,100 grm. Microscopic examination showed large amounts of fat stainable with Sudan III.

Chemical analysis of faeces under the experimental conditions given by Thaysen shows:—

Weight of faeces per 24 hours	465	gram.
Dry substance	84.6	"
Total fat output	30.7	"
Neutral fat	10.7	"
Free fatty acids	8.4	"
Soaps	11.6	"
N output in faeces	4.9	"

These findings show a great increase in the fat output and a slight increase in the output of nitrogen with the faeces. Numerous examinations of the stools failed to reveal any blood, mucus, or pus.

Ewald test meal. Amount 50 + 42 c.c., well chymified; mucus; Congo 45; phenolphthalein 57.

Blood-pressure: 110/60. *Sedimentation test:* 7 mm. *Basal metabolism:* 110 per cent.

Glucose tolerance test (ingestion of 70 grm. glucose): fasting blood-sugar 74 mg. per cent.; blood-sugar determined every fifteen minutes after intake of glucose: 88, 97, 88, 84, 86, 81, 79, 74, 68 mg. per cent. Greatest increase of blood-sugar value: 23 mg. per cent.

Fat tolerance test [Lawaetz and Vogt-Möller (22), with intake of 100 gr. olive oil] performed on 7 December 1935, after the patient had improved considerably:

Blood-fat value, fasting	0.44	gram. per 100 c.c. blood
" " after 2 hours	0.63	" "
" " " 4 "	0.67	" "
" " " 6 "	0.56	" "
" " " 8 "	0.56	" "

These are normal values.

Serum calcium. 9.3 mg. per cent. *Serum phosphorus:* 2.93 mg. per cent.

X-ray examination. *Forearms and hands—legs and feet:* the bones were somewhat delicate, but there was no halisteresis. *Stomach and duodenum:* no abnormality. *Intestines, seven hours after contrast meal:* the small intestine was completely empty of the contrast meal. The whole contrast meal filled the colon from the caecum to the lower part of the descending colon. The right flexure was seen at the level of the iliac crest. *Colon, after barium enema:* no sign of stricture. The sigmoid and lower part of the descending colon were filled rather poorly and the haustrations were irregular, undoubtedly due to spasm (colitis?). The ascending and transverse colon was somewhat dilated.

Blood examination. Hb.: 83 per cent.; red-blood count: 3,900,000; colour index: 1.09; volume percentage: 30; volume index: 0.89; white-blood count: 8,000; platelets: 220,000; reticulocytes: 0.5 per cent.; blood smear: marked anisocytosis, otherwise no abnormality of the red cells. Price-Jones curve: mean diameter 7.083μ , σ 0.84μ , v 11.9 per cent.; microcytosis 1.8 per cent.; megalocytosis 1.4 per cent.; differential count: neutrophile leucocytes 68 per cent.; eosinophils 1 per cent.; lymphocytes 26 per cent.; monocytes 5 per cent.

Treatment. Low fat diet + Be vital (vitamin B preparation manufactured by the Leo Chemical Works, Copenhagen).

On her discharge the patient had improved greatly, she was not tired or nervous, her appetite was good, and the meteorism was not so severe (circumference of the abdomen, in the morning 74 cm., in the evening 77 cm.); she had also gained considerably in weight. The stools were formed, one or two a day, normal in colour and containing but little fat. The pigmentation of the face had subsided, and the stomatitis had improved considerably, although some small aphthae still appeared now and then.

After her discharge from the hospital, the patient continued to take the low fat diet together with vitamin tablets (A, B, C, and D, two tabl. \times 3) and *calcei lactas* (1 gm. \times 3), and she continued feeling well.

Re-examination, 2 September 1936: she looked healthy, faint pigmentation of the face. Hb.: 90 per cent. Defaecation once daily; stools formed, normal in colour, macroscopically not fat-containing.

Summary of case record. A woman, aged 27, who had never been in the tropics and gave a past history of good health, noticed in the middle of pregnancy that her stools were for some time of a lighter colour and more frequent than normally. Shortly after, a severe degree of anaemia developed and there appeared a pigmentation of the face together with aphthous stomatitis. The anaemia improved after blood transfusion and treatment with iron and liver extracts. The stools were transitorily voluminous. Labour and puerperium proceeded normally. Two to three months post partum there developed a typical idiopathic steatorrhea: fatty diarrhoea with stools of quite the same character as seen in tropical sprue, with a great increase of the fat output and a slight increase of the nitrogen output, low blood-sugar curve in the glucose tolerance test, meteorism, pigmentations, aphthous stomatitis. Under treatment with a low fat diet (with addition of vitamins) there was a very marked improvement which has persisted since her discharge from the hospital—six months ago.

Comments

There can be no doubt about the correctness of the *diagnosis* 'idiopathic steatorrhea'. In the differential diagnosis there would hardly be any reason to consider other conditions than pancreatogenous steatorrhea, and this possibility is decisively contradicted by the low blood-sugar curve and the *slight* increase in the faecal output of nitrogen, for pancreatogenous fatty diarrhoea is associated with a diabetic or normal blood-sugar curve and a far greater nitrogen output in the faeces.

The *case record* presents several points of interest:

1. *Anamnesis.* It is certain that in this case the disease did not make its appearance until the patient was twenty-seven years old. The patient is a near relative of the writer, and it is fully established that previously she had never been troubled with any intestinal disorder of a similar nature as seen in her present illness. As mentioned before, Bennett, Hunter, and Vaughan (4) are inclined to deny the existence of idiopathic steatorrhea arising in adults (non-tropical sprue) as they claim that thorough questioning about the past history of the patient will invariably reveal that the affection can be traced back to similar phenomena in childhood, possibly

combined with rickets and infantilism. In a subsequent paper, Bennett (3) has described a case of the disease, developing at the age of fourteen years, which speaks in favour of Thaysen's view; Bennett emphasizes, however, that there was no stomatitis in this case and that the stools did not look like the faeces usually found in tropical sprue. In the case here reported the clinical picture of the disease differs in no respect from that of tropical sprue; that the growth of this patient in childhood and adolescence had been perfectly normal, without any sign of previous rickets or inhibition of growth, is evident from the photos (Plate 4, Figs. 1 to 3), which form a striking contrast to those illustrations of patients with infantilism and monstrous bone deformities that are presented in the paper of the authors mentioned above.

2. *Development of the disease during pregnancy.* According to van der Burg (5) and Krjukoff (21), there is some connexion between pregnancy and the development of tropical sprue. Manson Bahr and Willoughby (24) subscribe to this view, and they report two cases of tropical sprue which occurred in direct connexion with pregnancy and two other cases in which pregnancy elicited a relapse of the disease. A similar connexion between pregnancy and non-tropical sprue has not been observed previously but may now be put down as an additional feature common to these two sub-groups of idiopathic steatorrhoea.

3. *Development of the disease.* This is marked by three phases: (a) The initial stage with fatty diarrhoea which is noticed but little at the time and is not mentioned at first. (b) The development of the extraordinarily severe anaemia which quite dominates the clinical picture of the disease and tends to conceal its other features. This is nothing new. In non-tropical sprue as well as in tropical sprue a hyperchromic anaemia may stamp the condition to such a degree that it is diagnosed as pernicious anaemia; and in two of Thaysen's cases the early stage of the disease was associated with such a marked degree of hypochromic anaemia that the morbid condition was interpreted as simple achylic anaemia.

In the present case it is only reasonable to consider pregnancy an essential factor in the production of anaemia; this is further suggested by the fact that functional examination of the stomach during the first admission of the patient showed a condition of hypochylia, whereas during her second admission, when there was only a slight degree of anaemia but a far more pronounced steatorrhoea, the gastric secretion was normal. Still, the character of the anaemia in this patient and its behaviour to treatment suggest the presence of some other factor besides pregnancy. The anaemia of pregnancy is most often hypochromic, less frequently hyperchromic, and in most cases it responds to iron or liver therapy. But this patient presented the picture of orthochromic normocytic anaemia which, to begin with, was quite refractory to iron and liver treatment, whereas the blood transfusion proved effective by stimulating a remission. (c) The fully developed, typical, clinical picture of idiopathic steatorrhoea.

4. *The favourable course.* It is quite true that the observation period (nine months) since her discharge from the hospital is rather short, but the patient had no relapse whatever during this period, and her general condition remained good. In comparison with the usual course of non-tropical sprue, the prognosis of which must be said in general to be poor *quoad restitutionem* and doubtful *quoad vitam*, this case illustrates strikingly the great importance of the early diagnosis.

Case 2. Male, aged 74. Family history negative.

The patient was a major-general, who had served in India and Burma for about eighteen years, but was always stationed in the hills. He left India in 1914. During the World War he was in Egypt, and since 1919 he had lived in Natal until he returned to England in 1935.

The patient gave a past history of good health except for typhoid fever in 1883, and malaria in 1885, without any permanent sequelae of these diseases—in particular, there were no other gastro-intestinal affections.

Since 1933 there had developed disease of the right hip, with pain and reduction of mobility; an advanced condition of osteo-arthritis was said to have been diagnosed.

In the summer of 1934 he began rather suddenly to suffer from diarrhoea, and the stools had since been loose and irregular. At the time of examination the bowels moved twice a day, once with fairly formed stools and once with very copious thin stools. The latter type of bowel movement announced its coming with a violently urgent desire to evacuate the bowels, so that he was afraid to go out till the defaecation was over. The stools were very light in colour, almost whitish, with foamy bubbles, but never with any admixture of blood. During the last year there had been only a brief period of normal defaecation; otherwise his condition had been unchanged. There had been a little abdominal discomfort, but no real pain. Two to three months previously his mouth became very sore, especially the inside of the lips, so that all food, and particularly wine and tobacco, gave intense burning.

The patient had been feeling very tired and he had lost a good deal in weight; at the same time he had noticed that his measurements at the tailor's had changed, his waist being somewhat greater and his chest measure smaller.

He has been treated with a liver preparation (liveroid), by mouth, and with iron for four months.

In the autumn of 1935 he consulted Dr. A. G. Gibson, Oxford, who made the diagnosis of sprue and obligingly furnished the following data of examinations:

Analysis of faeces:

Total fat content	46.14	gram.	in 100	gram.	dry substance
Neutral fat	6.54	"	"	"	"
Fatty acids and soaps	39.60	"	"	"	"

Blood examination. Hb.: 64 per cent.; red-blood count: 2,970,000; colour index: 1.1; white-blood count: 4,300; blood smear: anisocytosis and megalocytosis. Differential count: neutrophile leucocytes 69 per cent.; eosinophils 7 per cent.; lymphocytes 19 per cent.; endothelial cells 4 per cent.; mast-cells 1 per cent.

Sigma reaction. Negative; serum calcium: 9.8 mg. per cent.

Glucose tolerance test (after 50 gram. glucose):

Fasting blood-sugar concentration	95 mg. per cent.
Blood-sugar concentration after $\frac{1}{2}$ hour	100 " "
" " " 1 " "	125 " "
" " " $1\frac{1}{2}$ hours	100 " "
" " " 2 " "	98 " "

He was then referred to the Medical Department of the St. Elizabeth Hospital where he stayed from 28 Nov. 1935 to 11 Jan. 1936, and he was further under ambulant treatment till 8 April 1936.

Physical examination. The patient was rather thin and markedly anaemic. There was a slight icteric tint of the sclerae. A few pigmented spots, less than 2 cm. in diameter, were seen on the hands and legs; otherwise no pigmentation. Tongue: some atrophy of the mucous membrane in general; the tip and margins appeared red and irritated. Otherwise no affection of the oral mucosa. Auscultation of the heart and lungs gave normal findings. Abdomen: rather large and full in comparison to the rest of the body; slight meteorism; no tenderness or tumours. No enlargement of the liver or spleen. Extremities: marked limitation of the movements in the right hip joint; otherwise no abnormalities. Chvostek's and Trousseau's signs: negative. Weight: 68.0 kg.

Urine. No albumin or sugar. *W.R.:* negative. *Sedimentation test:* 15 mm.

Ewald test meal. Amount 68 + 50 c.c., coarsely chymified; no mucus; Congo 44; phenolphthalein 64.

Blood examination. Hb.: 78 per cent.: red-blood count: 3,000,000; colour index: 1.30; volume percentage: 36; volume index: 1.39; white-blood count: 4,200; blood smear: marked anisocytosis and megalocytosis; a few normoblasts. Differential count: neutrophile leucocytes 72 per cent.; eosinophils 1 per cent.; basophils 1 per cent.; lymphocytes 21 per cent.; monocytes 5 per cent. Reticulocytes: 1 per cent. Price-Jones curve: mean diam. 8.343μ ; σ 0.77μ ; v 9.2 per cent.; microcytosis 0.4 per cent.; megalocytosis 43.0 per cent. Icterus index (Meulengracht): 15.

Basal metabolism. 95 per cent.

Glucose tolerance test (ingestion of 70 grm. glucose). Fasting blood-sugar 104 mg. per cent.; blood-sugar determined every ten minutes after intake of glucose: 101, 111, 113, 127, 143, 132, 117, 108, 102, 97, 93 mg. per cent. Greatest increase of the blood-sugar value: 39 mg. per cent.

Fat tolerance test. Lawaetz and Vogt-Möller, with intake of 100 grm. olive oil:

Blood fat value, fasting	0.45 grm. per 100 c.c. blood
" " after 2 hours	0.52 " "
" " " 4 " "	0.56 " "
" " " 6 " "	0.67 " "
" " " 8 " "	0.56 " "

i.e. normal values. This test was made at a time when the steatorrhoea was less pronounced.

On admission the faeces were very light in colour, voluminous, thin or mushy, weighing up to 850 grm. per twenty-four hours.

Treatment. The patient was given a diet beginning with 1,500 c.c. milk and raw fruit, increasing gradually and extending to include chopped veal, eggs, bread, honey, marmalade, porridge, and fish. The anaemia was treated

with injections of liver extract (*Exhepa fortior*), at first 4 c.c. daily (till 1 Dec. 1935), then 2 c.c. daily (till 18 Jan. 1936), then at longer intervals (from 1 March, once a week). From 18 Jan. 1936 he was also given Bevitall (vitamin B), 1 teaspoonful thrice daily.

This treatment had an excellent effect. His tiredness disappeared, also the soreness of mouth. The stools became formed, reduced in amount, and far less fat-containing. The patient regained a normal control of the desire of defaecation. He gained 7.4 kg. in weight. He recovered from the anaemia, as shown by the following records:

	Haemoglobin %.	Red-blood cells (millions).	Colour index.	Volume %.	Volume index.
29.11.35	78	3.0	1.30	36	1.39
27.12.35	86	3.6	1.19	—	—
17.1.36	93	3.7	1.24	—	—
21.2.36	90	4.5	1.0	46	1.18
8.4.36	105	4.8	1.11	46	1.11

Price-Jones curve (Figs. 4 and 5)

	Mean diam.	σ	v	Microcytosis.	Megalocytosis.
29.11.35	8.343 μ	0.77 μ	9.2 %	0.4 %	43.0 %
8.4.36	7.441 μ	0.48 μ	6.5 %	0 %	0 %

Summary of case record. A man 74 years old, who had lived in India until 1914 and in Natal from 1919 to 1935, was in 1934 attacked by sprue with typical stools, meteorism, loss of weight, stomatitis, severe hyperchromic and megalocytic anaemia, and low blood-sugar curve. Under the treatment with a low fat diet, injection of liver extract (large doses) and peroral administration of vitamin B, there was a very marked improvement of all the symptoms—especially the anaemia, which recovered completely.

Comments

In this case the possibility of pernicious anaemia was the most important point to settle in the differential diagnosis. Examination of the blood showed hyperchromic megalocytic anaemia with a Price-Jones curve quite resembling the curve obtained in pernicious anaemia. Moreover, there was also hyperbilirubinaemia. This phenomenon has not been observed previously in non-tropical sprue, and it has been described in only a few cases of tropical sprue (Fairley, Mackie, and Billimoria (11), Krjukoff (21)), and in those instances it probably was due to a complication with malaria. (In this connexion it is surprising that Castle and his collaborators (7) find icterus in 42 per cent. of the sprue cases in Puerto Rico. The explanation of this presumably is to be looked for in the nature of the patient material, as will be mentioned later.) The slight degree of icterus found in this case places the anaemic condition nearer to pernicious anaemia. But there was no leucopenia, and the Ewald test meal showed normal acidity of the gastric secretion. In particular, the presence of steatorrhoea together with the typical low blood-sugar curve were decisive of the diagnosis, idiopathic steatorrhoea.

But, while there can be no doubt about the correctness of this diagnosis, the classification of the case may be open to discussion.

It is the case of a patient who had spent many years in the tropics, but

without having suffered from intestinal disorder. He had lived only in mountain districts, but he had never suffered from 'hill diarrhoea'—an affection closely related to, and possibly identical with, sprue. His illness made its appearance in Natal, twenty years after he had left the tropics. This fact, it is true, may hardly exclude the possibility of tropical sprue in the present case, as the disease can remain latent for several years and manifests itself long after the patient has returned to a temperate zone—even after an interval of up to twenty years. Still, Manson-Bahr and Willoughby (24) state that a latent period of six to eight years is relatively common, whereas longer intervals are very rare. The present case may be interpreted in this way. On the other hand, as sprue originating in countries with a temperate climate is not so infrequent as assumed previously, the question rises whether it is justified as a rule to look upon cases of this kind as originating from the tropics merely because the patients have stayed in the tropics many years before. This argument has been advanced by Thaysen, and, according to his view of these points, the present case is classified as non-tropical sprue, originating in Natal. This makes it the first case of sprue reported as originating in Natal—according to an obliging communication from Dr. H. Harold Scott (26), Director of Bureau of Hygiene and Tropical Diseases, London. On the whole, sprue is of rare occurrence in Africa, although an increasing number of cases are reported from Kenya (Scott (26)), and Manson-Bahr (23) has reported a single case from Nyasaland. So it appears as if a gradual decrease in the frequency of sprue from tropical to temperate regions may be observed also in Africa.

The course of the disease showed the most favourable effect of parenteral administration of liver extract as compared to the slight effect obtained with peroral liver therapy through a considerable length of time. There was a complete remission of the anaemia. Normal values were obtained for the haemoglobin percentage, red-blood count, and volume percentage; the same applies to the diameter of the red cells, as the pernicious-like Price-Jones curve became quite normal: normal mean diameter and variation coefficient, no micro- or megalocytosis (Figs. 4 and 5).

The effect of the liver therapy upon the hyperchromic anaemia in sprue is well established. Recently it was confirmed by Castle, Rhoads, Lawson, and Payne (7), who in their report of 92 cases of sprue in Puerto Rico have emphasized in particular the value of the parenteral administration of liver extract. From their therapeutic results these authors draw some very far-reaching aetiological conclusions, defining tropical sprue as a deficiency disease closely related to pernicious anaemia. In both of these morbid conditions, the authors say, there is a defective reaction between extrinsic and intrinsic factors; in some cases both the factors are lacking, in others the wanting of one factor is predominating; defective absorption from the gut is probably present in some instances.

The work of Castle and his collaborators has been criticized rightly by

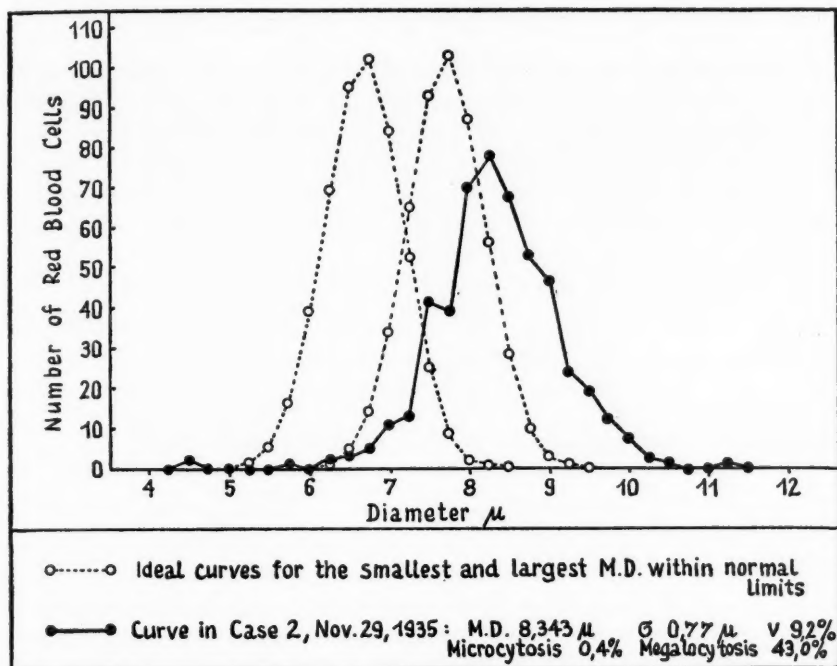


FIG. 4. Patient No. 2. Price-Jones curve, November 29, 1935.

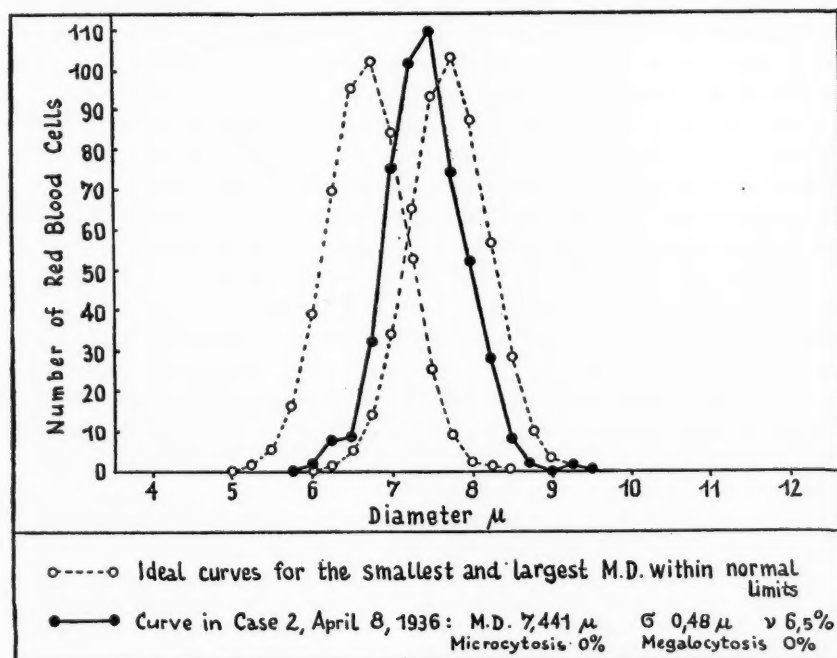


FIG. 5. Patient No. 2. Price-Jones curve, April 8, 1936.

Hansen and v. Staa (16), who claim that Castle and his associates make the diagnosis of sprue on patients with glossitis, hyperchromic anaemia, and bilirubinaemia, but without diarrhoea, let alone the typical fatty stools which—in contrast to the hyperchromic anaemia—constitute a *conditio sine qua non* in cases of sprue. On the whole, it is rather difficult to understand how it is possible to disregard the great difference in the clinical features of most of the cases of these two diseases. A comparative tabulation of the main symptoms of the two diseases will illustrate this point plainly:

	<i>Sprue.</i>	<i>Pernicious anaemia.</i>
Achylia	Inconstant	Constant
Anaemia	Not constant, sometimes hyperchromic, sometimes hypochromic	Hyperchromic
Leucopenia	Rare	Constant
Icterus	Rare	Almost constant
Nutrition	Lowered	Normal
Stomatitis	Aphthous	Rather rare, most often only glossitis
Meteorism	Present	Absent
Stools	Steatorrhoea	Sometimes diarrhoea
Blood-sugar curve	Low	Normal or slightly hyperglycaemic

The pronounced difference between the typical cases of the two diseases does not exclude the fact that in mild cases of sprue with stomatitis and anaemia it may be very difficult to differentiate this condition from pernicious anaemia. But to generalize from this to the conclusion of the same aetiology in both diseases would quite break down the definition of these two clinical concepts and bring about, among other things, the bold hypothesis that also coeliac disease (Gee-Herter's disease) and pernicious anaemia aetiologically were closely related conditions.

The studies of Castle and collaborators on the presence of an intrinsic factor in the development of sprue are very interesting, but their significance is invalidated by the fact that in many cases the diagnosis of sprue is made in the absence of that essential criterion. It is only reasonable to imagine that the hyperchromic sprue anaemia may be brought about by: (1) lack of the extrinsic factor because of inadequate diet; (2) lack of the intrinsic factor; and (3) defective absorption of the anti-anaemic principle. That the first and the last of these possibilities are more important is suggested by the following facts:

1. In some patients with idiopathic steatorrhoea marmite is just as effective as peroral liver therapy (Vaughan and Hunter (32), Castle and Rhoads (6)), but in pernicious anaemia it is far inferior to peroral liver therapy (Davidson (9)).

2. Peroral liver therapy is more inferior to parenteral treatment in sprue than in pernicious anaemia.

Case 3. Woman, aged 38, married. Admitted to the Medical Department of the St. Elizabeth Hospital on 14 March 1936, with the diagnosis of tetany; neuromyalgia.

Previously the patient had been under treatment in other hospitals, several times under various diagnoses:

1. 1918, in a department of dermatology for prurigo atypica with pigmentation.

2. 1927, in a department of neurology under the diagnosis of neurasthenia; anaemia (slight); gastritis; encephalitis (?). In the case record it says that the bowels were regular and the faeces normal throughout her stay in the hospital.

3. 1930, in a department of neurology under the diagnosis of tetany. Nothing said in the record about steatorrhoea.

4. 1931, in a department of neurology for three months, referred to it by the Invalidity Insurance Court. Diagnosis: tetany (latent); hyperthyroidism; neurasthenia. The case record says nothing about the faeces.

5. 1933, in a department of medicine for two months under the diagnosis: tetany; eczema of hands; emaciation; absence of knee-jerk. Here it was noted in the record that the stools were thin and greyish.

6. 1933, in a department of dermatology under the diagnosis of eczema sparsum. The stools were not mentioned in the record.

7. 1935, in a department of medicine for three months under the diagnosis of tetany; anaemia; suppurative otitis media. On admission the serum calcium concentration was 8.3 mg. per cent.; on discharge from the hospital it was 11.9 mg. per cent.—after treatment with ultranol, calcium, and parathyroid injections. The stools are said to have been normal. In 1933 she was granted invalidity insurance benefit.

The patient said she had been well during the first years of childhood, but she was not able to give any data on the time of dentition and beginning to walk; she thought, however, she was normal in these respects. She had always been very short in stature.

The menses did not commence till the age of sixteen; she had never been pregnant.

She thought her present illness dated from 1926, when she began to have attacks of tetany, and to which she had been subject since.

Concerning her bowels, the patient stated first they had been 'fairly regular'; still, the history of tetany for a good many years and her rather peculiar appearance suggested the possibility of idiopathic steatorrhoea, and she was questioned a little more closely about this point. And she stated, without hesitation and with positive assurance, that she had been suffering from periods of diarrhoea ever since she was eight years old, with up to four stools a day, thin or mushy, light in colour, and very voluminous. Between sixteen to eighteen years of age these periods of diarrhoea were more infrequent and less pronounced; in later years they had again been more frequent. During her various periods in hospital the stools had been as a rule fairly normal, so that the patient found no occasion to mention her bowel movements to the doctors; and, on the whole, she had never attached any particular importance to these phenomena.

There had been no abdominal pain, no meteorism or flatulence; and the patient had never noticed any blood or mucus in the stools. The periods of excessive defaecation were now and then associated with vomiting and occasionally with fainting—especially in childhood.

The manifestation of tetany commenced in 1926. They appeared as typical attacks of tetanic spasms of the hands (*main d'accoucheur* position). There had been no spasms of the feet, larynx, or general convulsions. The attacks have lasted from half an hour up to several hours; the last attack, five days before the admission, lasted twenty-four hours. The attacks were

always more pronounced in the winter and spring. In the summer of 1935 the patient was almost free from such attacks, which could be elicited only after she had worked a long time with her hands. She thought she had noticed that cold and work were eliciting factors. She had often been treated with calcium, vitamin D (cod-liver oil, ultranol), and parathyroid preparations. The treatment had usually been fairly effective, but not lately, when she had had many attacks in spite of calcium therapy.

The patient had been anaemic for many years; in 1926, she said, her haemoglobin percentage was 60.

Now and then there had been an eruption of small reddish blebs along the margins of the tongue, and a burning sensation of the tongue during meals. She had lost considerably in weight—about 10 kg. since 1927. She complained of marked tiredness and pains in her legs, especially on walking. She had never noticed any haemorrhages in the skin or mucous membranes; she did not think there was any night blindness. Until 1926 she had been perfectly capable of work (house-work); since then her working capacity had been decreasing steadily, and three years ago she was granted invalidity insurance benefit.

Physical examination. The patient was very short, of infantile habit, pale, and thin. Mentality normal. No rachitic stigmata. She was freckled, and there was distinct symmetrical pigmentation at the corners of the mouth, along the margins of the lower jaw, on the neck, on the forearms, and on the volar surface of the wrists. On the dorsum of the right foot there was an eczematized pigmented area, about $1\frac{1}{2}$ cm. in diameter. There was a distinct *linea fusca*. The hair was normal. Height: 148 cm. Weight: 41 kg.

The tongue showed a slight atrophy of the mucous membrane, and there was a single aphthous patch on its tip. The teeth were defective. There was no enlargement of the thyroid. No swelling of peripheral lymph glands. Auscultation of the heart and lungs showed normal conditions. The abdomen was slightly distended, without tenderness on palpation or tumour. The circumference of the abdomen was 68 cm. in the morning, 73 cm. in the evening.

Extremities. Marked clubbing of the finger-tips. There was a slight reduction of the mobility in the left hip joint, and the movements were painful. The other joints were normal. Knee-jerks sluggish on the right side, lively on the left. Chvostek's and Trousseau's signs strongly positive.

Urine. No albumin, no sugar. *W.R.:* negative. *Sedimentation test:* 10 mm. *Blood-pressure:* 110/50. *Pirquet reaction:* ++.

Ewald test meal. Amount 35 c.c., well chymified; mucus present; Congo 63; total acid 89.

Blood examination. Hb.: 64 per cent.; red-blood count: 4,500,000; colour index: 0.72; volume percentage: 32; volume index: 0.82; blood smear. No anisocytosis; no micro- or megalocytosis; no polychromasia; no nucleated red cells. Price-Jones curve: mean diameter $7.130\ \mu$; $\sigma\ 0.86\ \mu$; $v\ 12.1$ per cent.; microcytosis 0.8 per cent.; megalocytosis 0. White-blood count: 7,400. Differential count: neutrophile leucocytes 55 per cent.; lymphocytes 42 per cent.; monocytes 3 per cent. Icterus index (Meulengracht): 3.

Blood urea: 12 mg. per cent.; *serum calcium:* 7.98 mg. per cent.; *serum phosphorus:* 3.8 mg. per cent.

Basal metabolism: 120 per cent.

Faeces. Light in colour, distinctly fat-containing, mushy or formed, varying in amount from 50 grm. to 700 grm.; as a rule the bowel moved once a day. No blood, mucus, or pus in the stools.

Chemical analysis of faeces under the experimental conditions given by Thaysen:

Weight of faeces per 24 hours	150.0 grm.
Dry substance " "	40.3 "
Total fat output " "	19.0 "
Neutral fat	5.7 "
Free fatty acids	4.7 "
Soaps	8.6 "
N output in faeces,, "	1.1 "

Peroral glucose tolerance test (ingestion of 50 grm. glucose). Fasting blood-sugar 80 mg. per cent.; blood-sugar determined every 10 minutes after intake of glucose: 80, 110, 110, 90, 95, 70, 85, 90, 90 mg. per cent.; greatest increase of blood-sugar value: 30 mg. per cent. (Fig. 6).

Intravenous glucose tolerance test ad mod. Jörgensen (18, 19) (intravenous injection of 20 grm. glucose) (Fig. 7):

	Blood-sugar mg. per cent.
Fasting	105
Immediately after the injection of glucose	235
3 minutes	215
6 " " "	205
9 " " "	190
12 " " "	175
15 " " "	160
30 " " "	140
45 " " "	110
60 " " "	90
75 " " "	90

Maximal value, 235 mg. per cent.; length of curve, 48 min.; areal figure, 24 sq. cm.; loading figure 72.

Ophthalmologic examination. Vision 6/6, emmetropia. Ophthalmoscopic findings normal. Conjunctiva, cornea, chamber, iris—all normal.

Examination of Distinction Power.

Brightness.	18/9 D.	21/9: A-vital, 1 c.c.	22/9 D.	Increase.
8.0	< 1.75		1.75	$\frac{1}{2}$ degree
7.0	1.75		2.0	1 "
6.0	1.75		2.0	1 "
5.0	1.50		1.75	1 "
4.0	< 1.25		1.50	1 $\frac{1}{2}$ "
3.0	< 1.0		1.25	1 $\frac{1}{2}$ "
2.0	0.50		1.0	2 "
1.0	0.0		0.50	2 "
0.0			0.0	

(C. Edmund.)

Capillary resistance test (Göthlin): normal.

X-ray examination: stomach: no abnormality. *Two hours after contrast meal:* rather large retention in the stomach; otherwise the contrast meal appeared to be distributed in the small intestine throughout the abdomen. *Twenty-four hours after contrast meal:* no retention in the small intestine; the meal appeared to be located partly in the distal part of the transverse colon, partly in the rectum. *Colon, after barium enema:* no abnormality. *Fore-arms and hands—*as compared to the findings in control examination of a normal person of the same age, sex, and weight: distinct halisteresis. *Pelvis:* moderate halisteresis of pelvic bones, also of the femora.

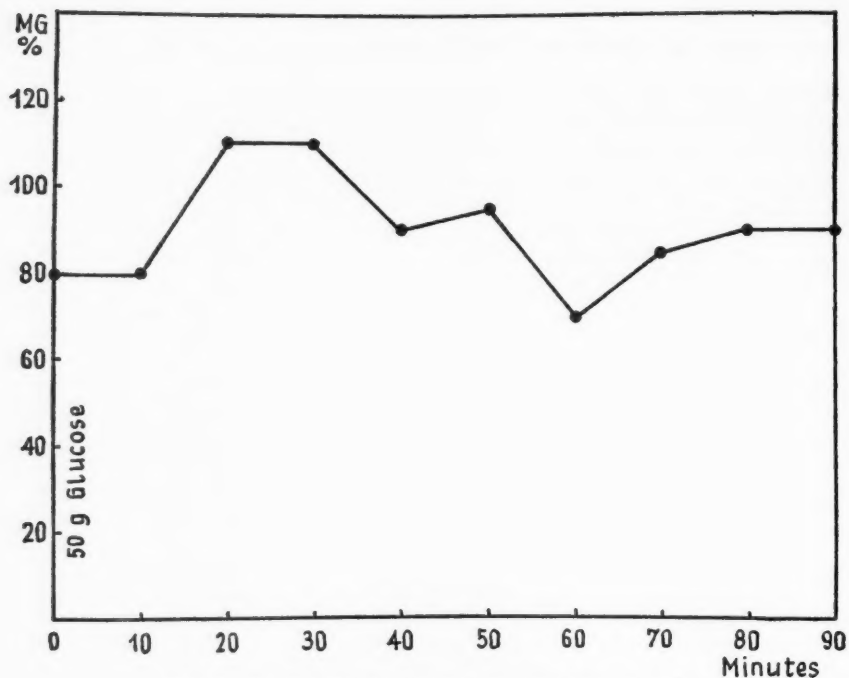


FIG. 6. Patient No. 3. Peroral glucose tolerance test.

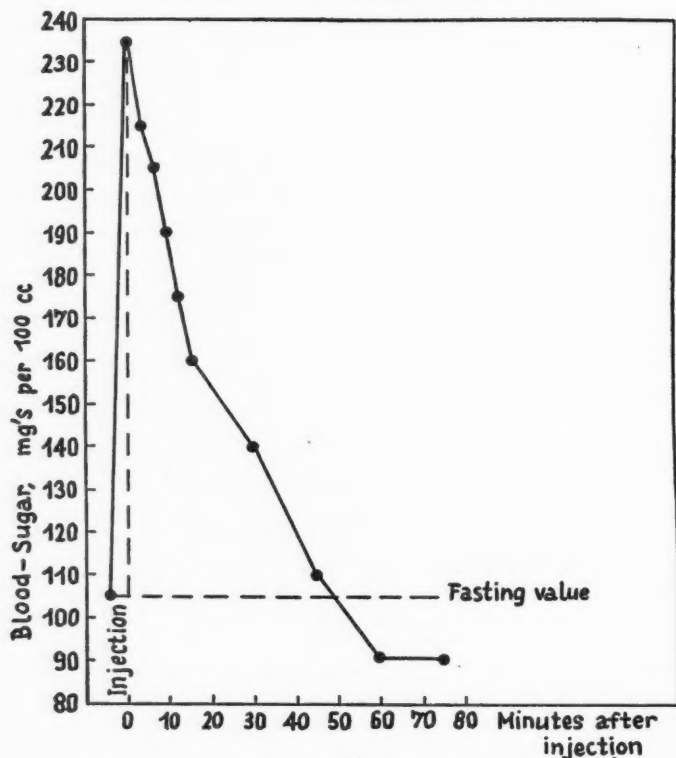


FIG. 7. Patient No. 3. Intravenous glucose tolerance test.

Treatment. The patient was given a low fat diet together with calcium lactate (1 grm. \times 3) and Ferrosi tartaras (0.5 grm. \times 3), besides injections of Decamin (altogether 8 \times 2 c.c.) and later on injections of vitamin A and D preparation for injection. As these injections (four altogether) were rather painful, they were discontinued, and from 11 May she was given a preparation of vitamin D, dissolved in alcohol, 10,000 units daily (the preparation was obligingly manufactured for this particular purpose by Ferrosan, Ltd.). In addition, from 9 May she was treated with the quartz lamp, and she was given Bevilal (2 teaspoonsfuls \times 2 daily).

Under this treatment she improved in several respects.

On 10 June the record says: 'The patient feels less tired and, on the whole, better than she has felt in the later years. There is only a little pain of the extremities. She walks much better, without support, and there is no limp. She has gained 2 kg. in weight. The pigmentation is less distinct; the linea fusca is not visible; the eczematized spot on the right foot has now become perfectly smooth, and there remains only a faint pigmentation. Chvostek's sign: +, but less marked. Trousseau's sign negative. The stools are mushy and formed, not particularly large, but still containing a considerable amount of fat. Serum calcium: 9 mg. per cent. Hb.: 76 per cent. Red-blood count: 4,000,000. Colour index: 0.95.'

On 29 June her condition was about the same as described above. Still, her general condition appeared to improve steadily—additional weight increase of 1 kg.—but the steatorrhoea was unchanged, and the anaemia improved but little. Therefore treatment with Exhepa fortior was now instituted, at first 2 c.c. daily, later 2 c.c. three times a week.

30 July. The patient was up and about, and out of doors, feeling well and tiring but little. No pain of extremities. Walking perfectly normal. Chvostek's sign weakly positive. Trousseau's sign negative. Weight: 45 kg.

Blood examination: Hb.: 84. Red-blood count: 4,500,000. Volume percentage: 35. Colour index: 0.93. Volume index: 0.90. Serum calcium: 9.7 mg. per cent. Defaecation: one or two stools a day; total daily amount 200–300 grm., mushy or formed, still voluminous and fatty.

Summary of case record. A woman, aged 38, receiving invalidity insurance benefit, and having been in hospital seven times previously for tetany, anaemia, skin affections with pigmentation, &c., entered this department with tetany. It was found that the underlying illness in her case was a typical idiopathic steatorrhoea, the history of which could be traced back to the age of eight years. She presented the following symptoms: infantilism, pigmentations, stomatitis, meteorism, steatorrhoea with greatly increased fat excretion and normal nitrogen output, hypocalcaemia, tetany, osteoporosis, clubbing of the fingers, hypochromic anaemia, low blood-sugar curve after ingestion of glucose in tolerance test, low blood-sugar rise, and short curve after intravenous injection of glucose.

Treatment with a low fat diet, calcium, vitamin B, vitamin D, quartz light, iron, and liver extract had a very favourable effect on the general condition, skin lesions, tetany, and anaemia, whereas the steatorrhoea was not influenced very much by the therapy.

Comments

The long history of the present illness in the case of this patient is typical in a certain sense. It is comparable with two of the cases reported by

Thaysen (30)—patients who had also been in hospital many times under various other diagnoses. All the symptoms presented by this patient and the various conspicuous sequelae, among which the tetany figured prominently, may be traced back and attributed to the underlying disease, idiopathic steatorrhoea. That this condition had not been recognized through so many years is not surprising. The patient had never been troubled very much by the steatorrhoea itself, and she did not consider herself ill before the severe tetany appeared in 1926. Furthermore, it seems as if her stools had been less abnormal during her periods in hospital than at other times. Only once, in 1933, was it noted that the stools were thin and greyish. At that time she had long been classified as a 'neurological' case, and the clinical picture of her illness was not revised. A case record such as the present illustrates urgently that the question of idiopathic steatorrhoea should be kept in mind, especially in cases associated with 'idiopathic' tetany and anaemia even though abnormalities of defaecation have failed to attract any particular attention, even from the patient. It has been emphasized repeatedly by Thaysen that this disease is too common to be considered a rarity. This is also evident from the fact that two of the cases here reported (Nos. 1 and 3) have been observed in this department within the last half-year, and it may be added that neither patient entered this hospital on account of the special interest the department is taking in the disease.

In the last patient the disease appears to have set in at the age of eight years. Hence it has to be designated as a somewhat late instance of coeliac disease. Idiopathic steatorrhoea may develop at any age, from the typical cases of coeliac disease at the usual age of one to five years, to cases like this and those reported by Gjörup (14) and by Bennett (3), that make their first appearance at the age of fourteen years, to the so-called non-tropical sprue, appearing in adults. Patient No. 1 furnishes a strikingly clear-cut instance of non-tropical sprue.

If any single feature in the clinical picture of the last patient were to be emphasized in particular, it is worth noticing that, besides the tetany as the most conspicuous symptom, the skin lesions have been so pronounced as to cause the patient to be warded twice in a department of dermatology, the first time at a relatively early stage of her illness. The pigmentation was not merely of the common type—probably due to vitamin B deficiency and related to the dermatoses of pellagra, as discussed by Thaysen (31)—but also eczematous or pruriginous skin changes with pigmentation. Similar skin symptoms have been described in idiopathic steatorrhoea by Bennett, Hunter, and Vaughan (4), Constam and Partch (8), and Konstam and Gordon (20). They differ from the skin lesions in pellagra in showing no tendency to localization to those parts of the body that are exposed to light. They probably are to be interpreted as expressions of a B-avitaminosis, resulting from defective absorption from the gut. In our patient there was an eczematous pigmented spot on the left foot which responded to

vitamin B treatment by becoming smooth, and leaving merely a faint pigmentation.

The low blood-sugar curve in the glucose tolerance test is reckoned as a cardinal symptom in idiopathic steatorrhoea. The explanation of this phenomenon is a question of considerable interest. Thaysen claims that it is due to an endocrine disturbance of the blood-sugar regulation, not to a defective absorption of glucose, and he finds support in the fact, that in these patients also, intravenous injection of glucose is followed by a low blood-sugar curve. In coeliac disease, this phenomenon has been demonstrated in one case by Andersen (1). In this patient, therefore, we also made a glucose tolerance test by the intravenous injection of sugar according to Jørgensen's (18, 19) method, and the test showed an abnormal curve (Fig. 7): maximal value only 235 mg. per cent. (normally 300–400 mg. per cent.); length of curve until establishment of the fasting value: 48 minutes (normally 90–100 min.). These findings speak clearly in favour of Thaysen's explanation of the phenomenon of the low blood-sugar curve.

In contrast, Ross (25) has recently reported some blood-sugar studies on children suffering from various diseases, including coeliac affection, in whom he found a combination of low peroral and high intravenous blood-sugar curves in the respective glucose tolerance tests. As Ross's paper is a preliminary report, an analysis of his findings will merely be preliminary too. Still, it is evident that several of the peroral curves which are characterized as low do not meet the requirement generally made of a low blood-sugar curve, namely, a rise that does not exceed the fasting value by 40 mg. per cent. Several of Ross's curves show a rise considerably higher than 40 mg. per cent., and far higher than observed in the cases reported by Svensgaard (27, 28). Cases of this kind are not suitable for a study of the genesis of the low blood-sugar curve, and it is hardly justified to conclude that coeliac disease is associated with a glycorrhoea analogous to the steatorrhoea.

For elucidation of this question from another angle, however, Badenoch and Morris (2) have given a significant contribution. They have shown that children with coeliac disease are more sensitive to the action of insulin than are normal children, as injection of insulin in children with this disease produces a greater blood-sugar fall than normally. The authors have then tried to treat such children with an anterior pituitary extract containing the contra-insular hormone, and the result was constantly: (1) increase of the fasting blood-sugar concentration; (2) normal instead of low blood-sugar curves in glucose tolerance tests (except in one instance, when this treatment had lasted only two days).

Badenoch and Morris attribute the low blood-sugar curve to carbohydrate fermentation in the bowel, as higher blood-sugar curves are obtained when carbohydrate tolerance tests are made with bananas, which hardly undergo any fermentation, than with glucose. The authors are therefore inclined to explain the low blood-sugar curve as dependent in part upon deficiency of

pituitary contra-insular hormone, while the duodenal secretion is influenced to such an extent as to cause an alteration in the physico-chemical conditions in the gut with inhibition of the glucose absorption.

This hypothesis thus represents a sort of compromise between the disputed explanations. It is a question, I think, whether it is really necessary in detail to interpret the results obtained by Badenoch and Morris as they do; but they seem to indicate that the low blood-sugar curve is ascribable to disturbances of the endocrine correlation.

A simple explanation of the low blood-sugar curve has been put forward by Himsworth (16 *a*) and later by Krarup and Gøtz (20 *a*), the latter authors giving a very detailed survey of the problem. These authors point out, how the previous diet may influence the shape of the curve, Himsworth (16 *b*), especially, gives proof of this theory. Diet poor in carbohydrate causes a high and protracted curve, whilst ample amounts of carbohydrate increase the tolerance, causing a low curve, corresponding to the curves found in cases of idiopathic steatorrhoea. A patient with idiopathic steatorrhoea will—on account of the impaired fat absorption, be forced to live largely on carbohydrates, and will therefore catabolize comparatively large amounts of carbohydrate.

Further, this explanation can only hold good if intravenous glucose tolerance tests show low curves. This seems to be the case, the results of Ross (25) therefore cannot be accepted.

The last patient is still in hospital under treatment. Her condition has improved considerably after about five months. But in view of the long duration of her illness, the prognosis must be made with reservation.

Her further *treatment* will have to be: 1. A low fat diet, as her fat absorption is constantly defective. 2. Iron. 3. Injection of liver extract. In this case it is true that the anaemia is hypochromic, but a rise of the haemoglobin percentage was accompanied by a decrease of the red-blood count, and this meant an indication for liver therapy that gives a pronounced favourable effect on the hyperchromic anaemia associated with idiopathic steatorrhoea. Under treatment with liver extract there has been a rise of the haemoglobin percentage and of the red-blood count up towards normal values, but as yet no effect on the steatorrhoea. 4. Vitamin A, in injectable form. A striking feature in the clinical picture of idiopathic steatorrhoea is the infrequency of symptoms of vitamin A deficiency as compared to the signs of vitamin D deficiency. *A priori* one would expect to find a lack of both of these fat-soluble vitamins—on account of the poor fat absorption, also because of the diet which deprives the organism of some of the richest sources of vitamin A. The reason why vitamin A deficiency has been demonstrated but seldom, however, may possibly be that the examination has been limited to the more conspicuous signs of such a condition (pronounced hemeralopia, conjunctival xerosis, &c.). It seemed desirable, therefore, to examine the patient thoroughly with a special view to the possible presence of an inconspicuous vitamin A deficiency, and Dr. C. Edmund was kind

enough to examine the distinction power of this patient according to Edmund and Clemmesen's (10) method. This showed that her distinction power was at the level which Edmund and Clemmesen designate as just below the normal zone. It is highly probable that there was some degree of faulty adaptation, and that this was due to vitamin A deficiency, for when she was given an injection of A-vital, no faulty adaptation could be demonstrated the next day, under the same conditions.

This result suggests that in future the patient should be given an injection of vitamin A at regular intervals.

As presumably several of her symptoms (stomatitis, abnormalities of the skin) are attributable to vitamin B deficiency, this with calcium should be included.

On the other hand, treatment with parathyroid hormone is to be looked upon as contra-indicated, even though the administration of parathyroid hormone may increase the blood calcium concentration and cause the tetany to subside—as has been done previously in this patient. The effect of the parathyroid hormone consists in a binding of the calcium in the blood, but this implies an increased risk of loss of calcium from the bones, giving osteoporosis and osteomalacia.

There are but few other diseases that have been given such an abundance of names. Thaysen introduced the designation 'idiopathic steatorrhoea' as a common class name for all three groups of Gee's disease, and, according to our present knowledge, this designation is very adequate, characterizing the disease by the primary and capital symptom, and differentiating it from steatorrhoea of other aetiology, especially pancreatogenous and enterogenous. In the introduction of this paper it is mentioned how very important the investigations reported by Thaysen have been to our knowledge of this disease. A documentation of this would be superfluous. Any investigator who in future will study the sprue-like diseases will have to accept Thaysen's work and add to it. It is therefore scientifically justified as well as practically expedient to associate Thaysen's name with the disease discovered by Gee, and employ the designation *Gee-Thaysen's disease* as synonymous with 'idiopathic steatorrhoea'.

Summary

A description is given of three new cases of idiopathic steatorrhoea:

1. Woman, aged 27, with a past history of good health, had in connexion with pregnancy a morbid condition that resembled tropical sprue. This case represents the non-tropical sprue in a remarkably pure form.

2. Man, aged 74, who had lived in the tropics till 64, now he has sprue after staying in Natal for fifteen years. This case is most probably to be interpreted as non-tropical sprue; if so, it is the first case reported from Natal. Besides the steatorrhoea, a hyperchromic megalocytic anaemia was

a predominant symptom. Treatment with diet and parenteral administration of liver extract gave excellent results, especially of the anaemia, which was cured completely. In this connexion the writer discusses the hypothesis advanced by Castle and collaborators about a common aetiology of sprue and pernicious anaemia, and emphasizes the difference between the clinical pictures of the two diseases in their typical forms.

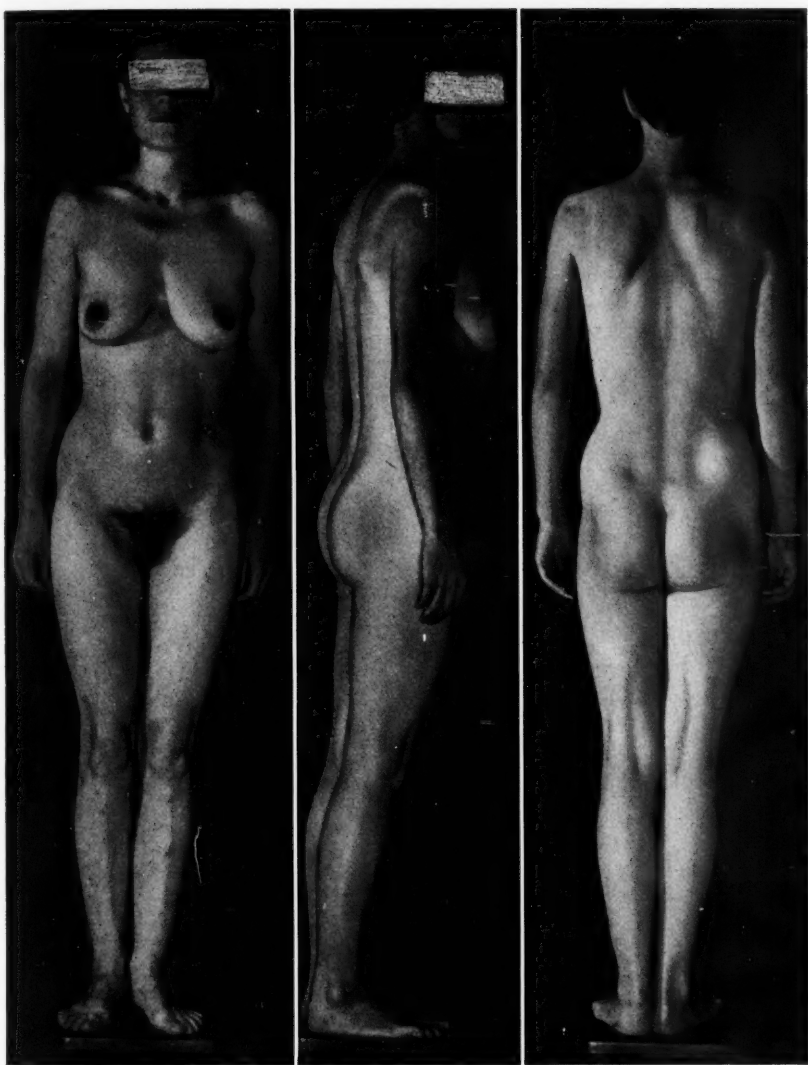
3. Woman, aged 38, who had been suffering from tetany for many years. The tetany was found to be due to idiopathic steatorrhoea setting in at the age of eight years. On the whole, the case record is typical, but the skin lesions were more pronounced than is usually seen. The patient showed a low blood-sugar curve in the glucose tolerance test, after intravenous injection of the sugar as well as peroral administration, corresponding to the view advanced by Thaysen: that the low blood-sugar curve is not due to defective absorption of glucose. In the discussion of this case, mention is made of the most recent studies on the genesis of the low blood-sugar curve.

4. The nomenclature is mentioned. In addition to the common designation 'idiopathic steatorrhoea' introduced by Thaysen, and comprising coeliac disease, tropical sprue, and non-tropical sprue, it is suggested to employ the name *Gee-Thaysen's disease*.

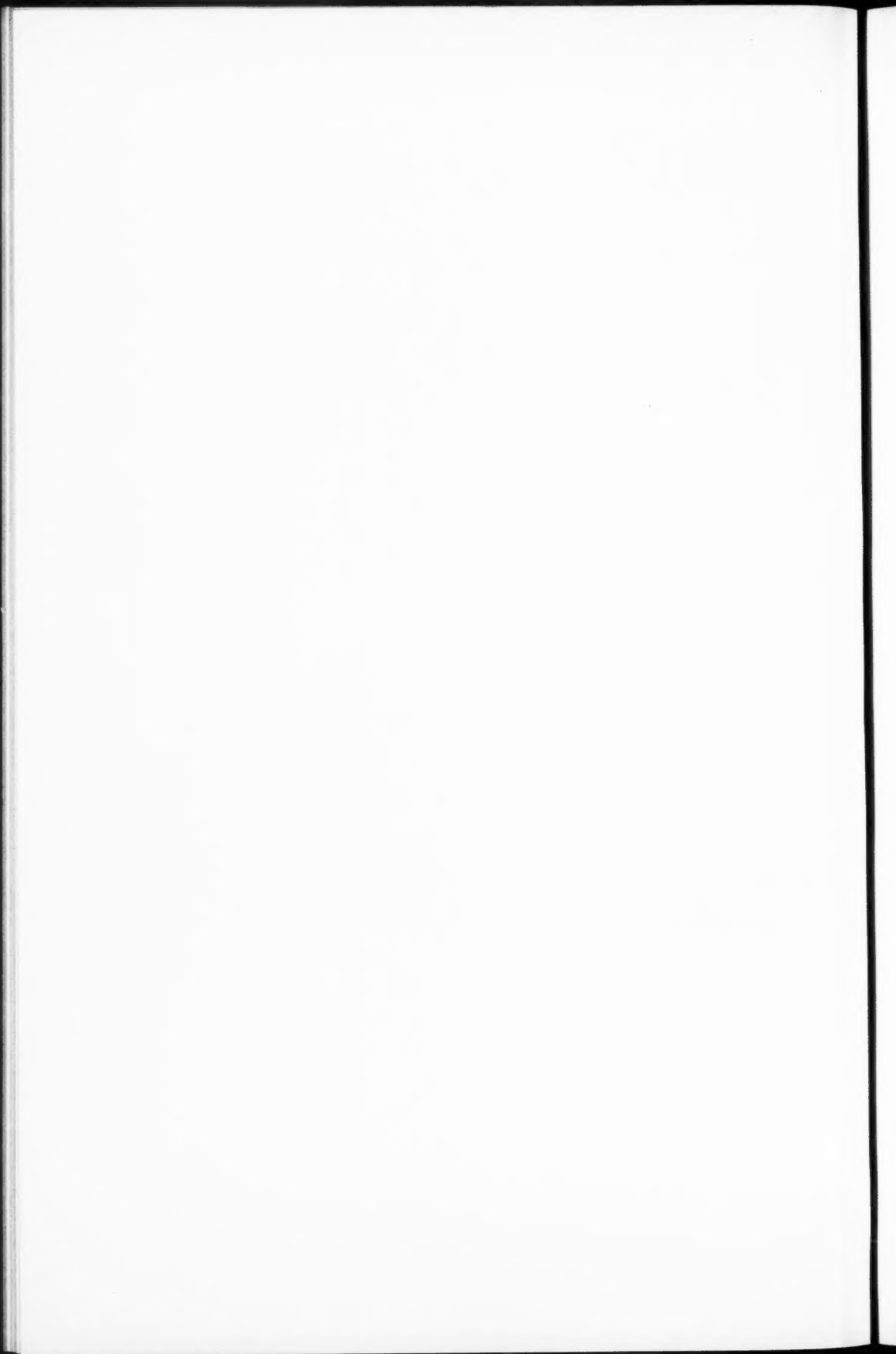
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FIGS. 1 to 3. Patient No. 1



THE HAEMOPOIETIC ACTIVITY OF THE HUMAN LIVER

PART II

ACHRESTIC ANAEMIA AND APLASTIC ANAEMIA¹

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IN a previous communication (7), investigations were reported on the haemopoietic activity of normal and abnormal livers taken from human subjects. The results as judged by clinical trial on cases of pernicious anaemia showed that the anti-anaemic liver principle was present in normal

TABLE I

Clinical Source of Liver.

Liver fraction.	Subject.	Cause of death.	Test case No.
L. I. 19	Untreated pernicious anaemia	Pernicious anaemia, cardiac failure, and pulmonary embolus	520
L. I. 22	Achrestic anaemia	Achrestic anaemia	480
L. I. 25	Aplastic anaemia	Aplastic anaemia	538
L. I. 26	Achrestic anaemia	Achrestic anaemia	116
L. I. 27	Aplastic anaemia	Achrestic anaemia	513
L. I. 29	Achrestic anaemia	Aplastic anaemia	543
L. I. 32	Achrestic anaemia	Achrestic anaemia	180
			581

human livers and in livers from treated cases of pernicious anaemia in active remission but was absent from cases of untreated pernicious anaemia in relapse. The significance of these results in the aetiology of pernicious anaemia was there discussed. Similar findings were reported shortly afterwards by Goldhamer et al. (1).

As opportunities have arisen during the last three years further data have been gradually collected in connexion with other diseases of the blood and blood-forming organs. The present paper deals with results obtained in achrestic and aplastic anaemias, since they throw further light on the relation of the liver to haemopoiesis.

Preparation and Clinical Testing of Liver Fractions

The liver extracts were prepared by the method given in the previous communication (Wilkinson and Klein, 1934). This method was employed

¹ Received January 18, 1937.

since it was thus possible to compare the potencies of the present with previous extracts, and because it was more convenient and economical to utilize them at this stage of preparation rather than lose valuable potency in further purification—the available supplies of these livers being so limited. Details of the method of clinical test are also described in the previous communication and it only remains to emphasize here once again the importance of choosing as test cases only suitably controlled patients with typical Addisonian pernicious anaemia. In the following sections the cases described conformed with these requirements and the case notes herein supplied are accordingly abbreviated. Since they constitute members of a large series of cases under investigation many other blood, metabolic, and gastro-intestinal investigations have been carried out on them but are omitted here, since they add nothing to the present discussion.

The extract for intramuscular injection was prepared in all cases by solution in the minimum amount of water and sterilization by filtration through the Seitz filter.

(a) *Fractions from livers from cases of achrestic anaemia. Fraction L. I. 22.* This fraction was supplied by patient W. K., and reference should be made to the very full report already published (Case I, *Quart. Journ. Med.*, 1936, v, pp. 82-6) for details of diagnosis, treatment, progress, and other findings.

At autopsy the liver weighed 1,720 gm. of which 1,430 gm. were employed and gave 18 gm. of fraction L. I. 22.

Test case P. A. 480. A housewife, aged 60 years, complaining of weakness, palpitation, dyspnoea, sore tongue, flatulent dyspepsia, diarrhoea, loss of weight, yellowish pallor. No neurological symptoms. Fractional gastric analysis showed achylia gastrica. Blood count (see Table II) (August 7, 1934). Red-blood cells, 1,930,000; white-blood cells, 6,200; haemoglobin, 50 per cent.; colour index, 1.3; polymorphonuclears, 59 per cent.; lymphocytes, 34 per cent.; large mononuclears, 3 per cent.; eosinophils, 4 per cent.; basophils, nil; very marked aniso- and poikilocytosis; no nucleated red cells; platelets reduced.

Sixteen gm. of this fraction L. I. 22 (equivalent to 1,270 gm. fresh liver) were given intramuscularly to case P. A. 480 during a period of five days producing a fair haematological response with a maximum of 25.8 per cent. reticulocytes on the tenth day (Table II). After the effects of this fraction had passed off the patient was used for the examination of further extracts by the method of the double reticulocyte response; these have no bearing on the present considerations and details are omitted.

Fraction L. I. 26. J. F., a night watchman, aged 62 years, was first seen on November 27, 1933, and had been diagnosed as achrestic anaemia. The full case notes and details of his treatment, progress, and post-mortem findings have already been described (Case II, *Quart. Journ. Med.*, 1936, v, pp. 88-93).

At autopsy the liver weighed 2,200 gm. and 2,000 gm. were utilized in the preparation of 31 gm. of fraction L. I. 36.

Test case P. A. 513. A railway inspector, aged 54 years, was admitted to hospital complaining of weakness, palpitation, dyspnoea, loss of weight,

sore tongue, flatulent dyspepsia, and increasing yellow pallor. There were no marked neurological symptoms. Examination revealed glossitis, enlarged spleen, achylia gastrica, and blood counts typical for pernicious anaemia

TABLE II
Test Case P. A. 480.

Date.	Retics. %	Red-blood cells per c.mm.	Haemoglobin %	Treatment.
7.8.34	1.0	1,930,000	50	Control period. No treatment.
8 "	0.9			
9 "	—			
10 "	1.0			
11 "	0.7			
12 "	0.9			1 grm. L. I. 22
13 "	0.8	1,460,000	43	
14 "	—			
15 "	2.8			
16 "	2.8			
17 "	6.6			5 "
18 "	7.2			Nil "
19 "	—			"
20 "	11.2	1,120,000	35	"
21 "	14.6			"
22 "	25.8			"
23 "	21.6			"
24 "	12.8			"
25 "	12.0	1,660,000	41	"

TABLE III
Test Case P. A. 513

Date.	Retics. %	Red-blood cells per c.mm.	Haemoglobin %	Treatment.
7.2.35	—	1,630,000	50	Control period. No treatment.
8 "	2.2			
9 "	2.7			
10 "	2.6			
11 "	0.8			
12 "	0.8			1 grm. L. I. 26
13 "	—			
14 "	0.8	1,460,500	42	
15 "	—			
16 "	1.8			
17 "	—			2 "
18 "	7.0			3 "
19 "	18.4			4 "
20 "	30.4			Nil
21 "	17.0	2,600,000	50	"
22 "	6.8			"
23 "	6.4			"
24 "	—			"
25 "	2.8			"
26 "	—			"
27 "	0.8			"
28 "	0.5	2,700,000	65	"
7.3.35	0.4	3,130,000	62	"
14 "	0.1	3,800,000	75	"
21 "	0.1	4,350,000	81	"

(see Table III). Blood count (February 7, 1935): red-blood cells, 1,630,000; white-blood cells, 7,000; haemoglobin, 50 per cent.; colour index, 1.5; polymorphonuclears, 65.5 per cent.; lymphocytes, 31.5 per cent.: large mononuclears, 2.5 per cent.; eosinophils, 0.5 per cent.; basophils, nil; no

nucleated red cells; very marked aniso- and poikilocytosis, platelets diminished in numbers.

He received 10 grm. of this fraction L. I. 26 (equivalent to 660 grm. fresh liver) intramuscularly during a period of four days. There was a very good response, a maximum of 30.3 per cent. reticulocytes being reached on the sixth day, while the blood count continued to improve for over five weeks without further treatment. (Table III.)

TABLE IV

Test Case P. A. 180

Date.	Retics. %	Red-blood cells per c.mm.	Haemoglobin %	Treatment.
4.5.35	0.6	1,650,000	34	Control period. No treatment.
6 "	0.5			
8 "	0.3			
10 "	0.5			
11 "	0.5	1,200,000	30	
12 "	—			
13 "	0.2			1 grm. L. I. 29
14 "	0.2			
15 "	0.3			
16 "	0.3			
17 "	2.0			
18 "	15.8	1,220,000	27	
19 "	37.2			4 "
20 "	19.0			4 "
21 "	30.2			4 "
22 "	17.2			Nil
23 "	14.2			"
24 "	13.1			"
25 "	10.8	2,060,000	48	"
1.6.35	0.8	2,900,000	62	"
11 "	0.9	3,320,000	68	"

Fraction L. I. 29. H. P., a gardener, aged 46 years, was diagnosed as achrestic anaemia after admission to hospital on March 29, 1934. (Case history and details recorded as Case 4, *Brit. Med. Journ.*, 1935, i. 194).

The liver weighed 2,300 grm. and 2,100 grm. were utilized to yield 77 grm. of fraction L. I. 29.

Test case P. A. 180. A glassblower, aged 70 years, was admitted to hospital complaining of weakness, palpitation, dyspnoea, loss of weight, soreness of the tongue, diarrhoea, severe headaches, stiffness of the legs, and paraesthesiae in the arms and legs, with increasing jaundice. Examination showed pale yellow colour of the skin; marked anaemia; no enlargement of spleen or liver; absent knee- and ankle-jerks, extensor plantar responses, achylia gastrica and blood counts as shown in the Table. Diagnosis: pernicious anaemia with spinal cord involvement. Blood count (May 4, 1935): red-blood cells, 1,650,000; haemoglobin, 34 per cent.; colour index, 1; white-blood cells, 4,200; polymorphonuclears, 53.5 per cent.; lymphocytes, 36.5 per cent.; large mononuclears, 6 per cent.; eosinophils, 4 per cent.; basophils, nil; very marked aniso- and poikilocytosis; six nucleated red cells per 200 leucocytes; very few platelets.

Twenty-two grm. of fraction L. I. 29 were administered parenterally over a period of seven days. A rapid response was obtained with a maximum reticulocyte peak of 37.2 per cent. on the sixth day (i.e. before all the fraction, which was obviously unnecessarily large, had been given), followed by a good response in the red-cell count and haemoglobin value.

THE HAEMOPOIETIC ACTIVITY OF THE HUMAN LIVER 147

Fraction L. I. 32. E. H., a housewife, aged 66 years, was diagnosed as suffering from achrestic anaemia. The full investigations and course of her condition have already been reported (Case 3, *Quart. Journ. Med.*, 1936, v, pp. 94-8).

At autopsy the liver weighed 1,600 grm., and 1,400 grm. were employed in the production of 18 grm. of fraction L. I. 32.

TABLE V
Test Case P. A. 581

Date.	Retics. %	Red-blood cells per c.mm.	Haemoglobin %	Treatment.
19.7.35	1.9	1,400,000	44	Control period. No treatment.
20 "	1.8			
21 "	—			
22 "	0.7			
23 "	1.0			
24 "	1.0	1,480,000	41	
25 "	—			
26 "	0.8			1 grm. L. I. 32
27 "	1.6			2 "
28 "	1.9			2 "
29 "	5.9			2 "
30 "	8.7			2 "
31 "	26.9			Nil
1.8.35	20.7	1,520,000	42	"
2 "	9.2			"
3 "	7.3			"
7 "	2.7	1,700,000	50	"
15 "	0.9	2,064,000	55	"
23 "	1.3	2,320,000	68	"
30 "	1.3	2,900,000	74	"

Test case P. A. 581. A laboratory assistant, aged 61 years, suffering from pernicious anaemia, was admitted to hospital complaining of dyspnoea, palpitation, vomiting, flatulence, loss of energy and weight, indigestion, soreness of the tongue, diarrhoea, jaundice, and some vertigo.

There was marked anaemia; no enlargement of liver and spleen; achylia gastrica and typical blood findings of pernicious anaemia. (See Table V.)

Blood count (July 19, 1935): red-blood cells, 1,400,000; white-blood cells, 6,000; haemoglobin, 44 per cent.; colour index, 1.6; polymorphonuclears, 77 per cent.; lymphocytes, 18.5 per cent.; large mononuclears, 2.5 per cent.; eosinophils, 2 per cent.; basophils, nil; marked aniso- and poikilocytosis; no nucleated red cells; platelets diminished in numbers.

He received 9 grm. of fraction L. I. 32 (equivalent to 700 grm. fresh liver) intramuscularly over a period of five days. There was a prompt haematological response, the reticulocytes rising to 26.9 per cent. on the sixth day, and although from our experience the red-cell count was slower at first in showing any marked increase (Table V), the patient continued to improve rapidly without further treatment.

(b) *Fractions prepared from livers from cases of aplastic anaemia.* *Fraction L. I. 25.* N. M., a housewife, aged 33 years, was admitted to hospital on January 30, 1935, in a collapsed condition with a history of intermittent bleeding from the rectum (haemorrhoids) and bruising of the limbs for some weeks. She was very pale, no jaundice, spleen, liver and glands were not enlarged, and there were some haemorrhages noted on both arms and legs. Some blood was passed per rectum on admission. Despite an immediate blood transfusion she died within a few hours.

Autopsy disclosed a complete aplasia of the marrow of the femur (shaft: a little fatty material; head: empty trabeculae), ribs and sternum, with haemorrhages into the cardiac, bladder, and uterine walls. Spleen (160 grm.): pulp was rather soft, hyperplastic. Liver was passively congested with small haemorrhages into the substance. The rectum appeared normal.

A diagnosis of aplastic anaemia was confirmed.

TABLE VI

Test Case P. A. 538

Date.	Retics. %	Red-blood cells per c.mm.	Haemoglobin %	Treatment.
18.2.35	1.7	1,550,000	45	Control period. No treatment.
19 "	1.8			
20 "	1.7			
21 "	1.5			
22 "	1.6			
23 "	1.0			
24 "	—			
25 "	1.4	1,170,000	36	1 grm. L. I. 25
26 "	1.3			2 "
27 "	1.6			3 "
28 "	4.1			Nil
1.3.35	10.6			
2 "	23.0			"
3 "	30.8			"
4 "	37.5	1,520,000	48	"
5 "	26.2			"
6 "	20.1			"
7 "	14.8			"
8 "	12.5			"
9 "	—			"
10 "	2.1			"
11 "	5.1	2,960,000	70	"
18 "	1.6	3,200,000	74	"
25 "	0.8	4,064,000	90	"

The liver weighed 1,600 grm., and 1,350 were utilized to produce 26.5 grm. of fraction L. I. 25.

This fraction is of special importance since no anti-anaemic treatment (other than blood transfusion) had been given to the patient, and the potency of the fraction cannot, therefore, be due to the previous administration of anti-anaemic preparations.

Test case P. A. 538. A housewife, aged 70 years, was admitted to hospital suffering from pernicious anaemia and cholelithiasis. She complained of weakness, palpitation, dyspnoea, nausea, vomiting, epigastric pain, flatulence, constipation, jaundice, loss of weight and appetite, and sore tongue.

There were no neurological symptoms. Achylia gastrica. Blood count (February 18, 1935): red-blood cells, 1,550,000; white-blood cells, 2,400; haemoglobin, 45 per cent.; colour index, 1.50; polymorphonuclears, 91 per cent.; lymphocytes, 7.5 per cent.; large mononuclears, 1.5 per cent.; eosinophils, nil; basophils, nil; marked aniso- and poikilocytosis; no nucleated red cells; platelets fairly scanty.

She was given 6 grm. of fraction L. I. 25 intramuscularly (equivalent to 305 grm. of fresh liver) over a period of three days. There was a very good haematological response, the reticulocytes reaching 37.5 per cent. on the seventh day (see Table VI), followed by a rapid increase in the red-cell count and haemoglobin value during the subsequent four weeks without further treatment (Table VI).

Test case P. A. 116. A collier, aged 69 years, was first diagnosed as a case of pernicious anaemia in 1930, but in consequence of his discontinuance of treatment was readmitted to hospital. There was still an achylia gastrica. Blood count (March 2, 1935): red-blood cells, 880,000; white-blood cells, 4,200; haemoglobin, 28 per cent.; colour index, 1.55; polymorphonuclears, 50 per cent.; lymphocytes, 37 per cent.; large mononuclears, 10 per cent.;

TABLE VII
Test Case P. A. 116

Date.	Retics. %	Red-blood cells per c.mm.	Haemoglobin %	Treatment.
28.2.35	1.0	1,100,000	30	Control period. No treatment.
2.3.35	1.7	880,000	28	
3 "	0.6		2	2 grm. L. I. 25
4 "	1.0	740,000	24	4 "
5 "	7.2	980,000	28	Nil
6 "	23.8			"
7 "	37.7			"
8 "	33.4	1,330,000	32	"
9 "	29.6			"
10 "	18.8			"
11 "	22.5			"
12 "	19.2			"
13 "	15.0			"
14 "	11.2	2,280,000	52	"
15 "	7.9			"
16 "	4.7			"
18 "	2.4			"
21 "	1.0	2,440,000	56	"

eosinophils, 3 per cent.; basophils, nil; very marked aniso- and poikilocytosis; no nucleated red cells; scanty platelets.

He was given intramuscularly 8 grm. of fraction L. I. 25 (equivalent to 410 grm. fresh liver) distributed over a period of three days.

There was an excellent hematological response, the reticulocytes being 37.7 per cent. on the sixth day (Table VII), while the red-blood cells and haemoglobin rose steadily without any further treatment.

Fraction L. I. 27. V. S., a female clerk, aged 18 years, was admitted to hospital on February 18, 1935, suffering from aplastic anaemia. She had been complaining for six months of dyspnoea, palpitation, weakness, excessive fatigue, anorexia, constipation, slight loss of weight but no gastrointestinal symptoms, nausea, or vomiting. She was very pale and waxy in appearance. There was tachycardia (112), spleen and liver and glands not enlarged; Wassermann reaction negative; nervous reflexes present, slightly exaggerated. Blood count (February 22, 1935): red-blood cells, 1,120,000; white-blood cells, 2,400; haemoglobin, 22 per cent.; colour index, 1; polymorphonuclears, 30 per cent.; lymphocytes, 65 per cent.; large mononuclears, 4.5 per cent.; eosinophils, 0.5 per cent.; basophils, nil; no nucleated red cells; aniso- and poikilocytosis marked; platelets scanty.

She failed to respond to treatment which included blood transfusions, intensive iron therapy, besides parenteral liver extracts and the oral administration of hog's stomach over a period of four weeks, and died on March 17, 1935.

Autopsy: aplastic anaemia with evidence of severe anaemia in most of the organs. Some patches of broncho-pneumonia and haemorrhage in the right lung. Iron present in large amounts in liver and spleen. Marrow of

femur, ribs, and sternum quite aplastic without any evidence of blood formation.

The liver weighed 1,070 grm. and gave 9 grm. of fraction L. I. 27.

Test case P. A. 543. A tram-driver, aged 60 years, had lost a lot of weight and complained of severe dyspnoea, palpitation, lack of energy, indigestion, flatulence, constipation with occasional attacks of diarrhoea, soreness of the

TABLE VIII

Test Case P. A. 543

Date.	Reties. %	Red-blood cells per c.mm.	Haemoglobin %	Treatment.
21.3.35	0.9	1,776,000	46	Control period. No treatment.
23 "	0.9			
26 "	1.1			
28 "	1.0	1,650,000	46	
30 "	1.1			
1.4.35	1.9			
3 "	1.6			1 grm. L. I. 27 2 " 2 " Nil " " " " " " " " " " " " " "
4 "	2.4	1,484,000	42	
5 "	—			
6 "	3.6			
7 "	6.4			
8 "	7.4			
9 "	7.1			
10 "	7.6			
11 "	13.2	1,420,000	44	
12 "	23.8			
13 "	28.7			
14 "	21.0			
15 "	15.2			
16 "	12.8			
17 "	6.5			
18 "	3.2	2,270,000	61	

tongue, nausea, vomiting, loss of appetite, and pins and needles in the limbs and shoulders. Spleen and liver were enlarged. Achylia gastrica. Blood counts and other examinations confirmed the diagnosis of pernicious anaemia. Blood count (March 21, 1935): red-blood cells, 1,776,000; white-blood cells, 6,600; haemoglobin, 46 per cent.; colour index, 1.35; polymorphonuclears, 44.5 per cent.; lymphocytes, 50 per cent.; large mononuclears, 3 per cent.; eosinophils, 2.5 per cent.; basophils, nil; no nucleated red cells; very marked aniso- and poikilocytosis; platelets moderate in numbers.

He was given intramuscularly during three days 5 grm. of fraction L. I. 27 (equivalent to 595 grm. of fresh liver) with a good haematological response, the reticulocytes reaching 28.7 per cent. on the ninth day, while the red-blood cells and haemoglobin increased steadily without further treatment (Table VIII).

(c) *Fraction from untreated fatal case of pernicious anaemia with subacute combined degeneration of the spinal cord.* One example was described in the previous paper (Wilkinson and Klein, 1934) using fraction L. I. 3. The following similar fraction (L. I. 19) is inserted here as corroborative evidence.

Fraction L. I. 19. A. M., a housewife, aged 60 years, was admitted to hospital on February 6, 1934, suffering from pernicious anaemia and subacute combined degeneration of the spinal cord.

Her main symptoms were difficulty in walking for two years owing to spasticity and slurring of the feet, pains in the limbs, paraesthesiae in the feet and hands, and inability to use her fingers for finer movements; there

was some dyspnoea, palpitation, anaemia, increasing yellowness, loss of appetite, flatulence, dyspepsia, and constipation. Examination did not disclose any enlargement of the spleen and liver, anaemia and jaundice were moderate, there were haemic cardiac murmurs. In the nervous system the knee-jerks were absent, plantar responses extensor, no clonus; loss of vibration sense and sensation to pin-prick and light touch in the legs and feet,

TABLE IX

Test Case P. A. 520

Date.	Retics. %	Red-blood cells per c.mm.	Haemoglobin %	Treatment.
27.11.34	1.8	2,200,000	66	Control period. No treatment.
28 "	2.0			
29 "	1.8			
30 "	1.8			
1.12.34	1.9	2,100,000	66	
2 "	1.8			
3 "	1.7			
4 "	1.8			
5 "	1.9			
6 "	0.5			
7 "	0.5	2,240,000	66	1 grm. L. I. 19
8 "	1.2			2 "
9 "	1.9			3 "
10 "	1.5			2 "
11 "	1.8			Nil
12 "	2.8			"
13 "	1.8			"
14 "	1.6	2,200,000	65	"
15 "	1.1			4 c.c.) Commer-
16 "	—			6 c.c.) cial liver
17 "	0.6			6 c.c.) extract
18 "	5.2			Nil
19 "	4.3			"
20 "	7.6			"
21 "	12.0	2,350,000	66	"
22 "	7.4			"
24 "	6.1			"
28 "	1.8	2,800,000	80	"
2.1.35	2.1	3,300,000	88	Pepsac 30 grm.
23.1.35	—	4,850,000	90	daily

much diminished in the hands and arms. Muscular weakness was noted in the limbs. Fractional gastric analysis—achylia gastrica. Blood count: red-blood cells, 2,520,000; haemoglobin, 82 per cent.; colour index, 1.6; white-blood cells, 10,600; polymorphonuclears, 71.2 per cent.; lymphocytes, 25.6 per cent.; large mononuclears, 3.2 per cent.; eosinophils and basophils, nil; marked aniso- and poikilocytosis, platelets reduced in number; two nucleated red cells per 100 white-blood cells. Some diffuse polychromasia.

Before any treatment was instituted the patient died following a femoral thrombosis and pulmonary embolus.

Autopsy confirmed the diagnosis of pernicious anaemia, cardiac muscle failure, femoral thrombosis, and pulmonary embolus.

The liver weighed 1,000 grm. and gave 13.7 grm. of fraction L. I. 19.

Test case P. A. 520. A housewife, aged 66 years, admitted to hospital suffering from pernicious anaemia with dyspnoea, palpitation, yellow pallor, loss of weight, flatulent dyspepsia, sore tongue, paraesthesia in the right leg, foot, and hands. Fractional gastric analysis showed achylia gastrica. Blood count (November 27, 1934): red-blood cells, 2,200,000; white-blood cells,

6,600; haemoglobin, 66 per cent.; colour index, 1.50; polymorphonuclears, 50.5 per cent.; lymphocytes, 46.5 per cent.; large mononuclears, 3 per cent.; eosinophils and basophils, nil; aniso- and poikilocytosis marked; one normoblast per 100 white-blood cells; platelets scanty.

Eight grm. of fraction L. I. 19 (equivalent to 585 grm. liver) were given intramuscularly during a period of four days. There was no haematological response indicating absence of potency in this fraction. The patient, however, responded normally after the administration of 16 c.c. of a potent intramuscular liver preparation.

Discussion

Wilkinson and Klein (7), using the technique of the clinical test for haemopoietic activity, investigated the content of the liver antipernicious anaemia principle (or liver active principle as it is also termed) in ten separate fractions prepared from human livers. Fractions prepared from calf livers and from normal human livers were found to be of equal potencies in initiating remissions in test cases of relapsing pernicious anaemia. Using these two fractions as standards, it was shown that the liver fractions prepared from partially treated cases or from cases of pernicious anaemia in remission, but dying from other causes, showed a diminution of haemopoietic activity depending on the degree of treatment or remission. On the other hand, livers from untreated fatal cases of pernicious anaemia did not show haemopoietic activity when so tested. (Table X.)

These findings were in harmony with the view that pernicious anaemia develops or a relapse occurs in those patients in which the liver is depleted of its store of the 'liver antipernicious anaemia' principle.

Such an occurrence may arise in various circumstances, as for instance, a deficiency of diet or impairment of normal gastro-haemopoiesis. The latter would include absence of, or insufficient, gastric haemopoietin, failure of the specific anti-anaemia gastric reaction, failure of absorption from, or destruction in, the alimentary tract of the anti-anaemic principle or its precursor (7, 6). All these factors exert an effect on gastro-haemopoiesis at different stages up to the actual storage of the liver principle in the liver.

It was obvious that other factors might arise to interfere with the normal withdrawal of the liver principle from the liver depot, and its utilization for normal erythropoiesis in the bone marrow. Some indication of the existence of such factors has been furnished by the identification of a further small group of megalocytic anaemias—termed achrestic anaemia (2).

The clinical features of this anaemia are generally similar to those of pernicious anaemia but, in contradistinction to pernicious anaemia, the gastric secretion is apparently normal, and the liver contains the 'liver antipernicious anaemia' principle in normal amounts. It should be emphasized that the investigation of these patients showed that exposure to toxic substances or pathological changes in the liver could be excluded from their aetiology. The bone-marrow showed essentially the same changes as in

TABLE X

Comparison of Response to Various Liver Extracts given by Intramuscular Injection

Source of liver.	Test case No.	Liver fraction.	Doses of liver expressed in g. of fresh tissue.	Reticulocytes.		Initial values.	
				Max. %.	Day of treatment.	R.B.Cs. $\times 10^6$.	Hb. %.
*Calf	396	L. I. 10	1,000	54.7	9	0.760	19
	384	L. I. 2 + L. I. 6	1,235	42.0	11	1.390	35
*Normal human	392	L. I. 7	1,200	30.1	7	1.120	31
	398	L. I. 2	1,015	61.8	10	0.430	12
	388	L. I. 4	1,100	16.8	11	1.490	38
*Remitting pernicious anaemia	393	L. I. 8	900	8.7	6	1.280	43
	393	L. I. 13	1,830	16.2	8	1.540	47
	399	L. I. 9	1,300	34.8	7	0.580	17
*Partially treated pernicious anaemia	350	L. I. 1	600	10.7	8	1.750	48
Untreated pernicious anaemia	385	L. I. 3	690	No response	—	1.230	30
	520	L. I. 19	585	No response	—	2.240	66
Achrestic anaemia	480	L. I. 22	1,270	25.8	10	1.460	43
	518	L. I. 26	660	30.4	6	1.460	42
	180	L. I. 29	600	39.0	7	1.200	30
Aplastic anaemia	581	L. I. 32	700	26.9	7	1.480	41
	116	L. I. 25	305	37.7	6	0.880	28
	538	L. I. 25	410	37.5	7	1.170	36
	543	L. I. 27	595	28.7	9	1.480	46

* These figures are taken for comparison from the previous paper and it will be noted that the total dosages of liver used were much higher than the later ones.

TABLE XI

Comparison of Three Types of Anaemia

	Type.	Gastric secretion.	Effect of anti-anaemic treatment.	Anti-anaemic potency of the liver.	Bone marrow.	Probable cause of anaemia.
Pernicious anaemia	Megalocytic, hyperchromic	Achylia gastrica. Haemopoietin nil	Remissions initiated	Nil	Megaloblastic hyperplasia	Deficiency of haemopoietin
Achrestic anaemia	Megalocytic, hyperchromic	Normal	Slight temporary effects	Very good	Megaloblastic hyperplasia	Inability to utilise anti-anaemic liver principle stored in body
Aplastic anaemia	Usually normocytic and normochromic	Normal	None	Very good	Aplasia	Marrow dyscrasia. Cause unknown

pernicious anaemia; that is to say, a marked hyperplasia of megaloblasts with relative infrequency of other members of the red blood cell series; this differs from the bone-marrow in 'pseudo-aplastic' or 'aregenerative'

anaemias in which megaloblasts occur rarely, and even then in smaller numbers than erythroblasts or normoblasts.

An investigation of the haemopoietic potencies of liver fractions prepared from four cases of achrestic anaemia has been described in this paper. Reference to Table X shows that they are at least equal to those previously obtained with normal human and calf-liver fractions. In the same table are shown results obtained in three cases using liver fractions prepared from material supplied by two cases of typical aplastic anaemia. It will be noticed that these also possessed equally potent haemopoietic activities when tested clinically. A further case of untreated pernicious anaemia furnished another opportunity to confirm the absence of liver anti-anaemic principle in these patients (L. I. 19) (7).

It has thus been established that the antipernicious anaemia liver principle is present in the livers of patients suffering from achrestic and aplastic anaemias. Nevertheless, while the available liver principle is not utilized in either anaemias, the cause differs in each case. In classical aplastic anaemia suitable bone-marrow cells are not available for the liver principle to act; in achrestic anaemia the bone-marrow shows the characteristic picture of arrested megaloblastic maturation, in spite of the presence of adequate quantities of the liver principle which normally promotes maturation. In neither aplastic nor achrestic anaemias is there any apparent failure to produce haemopoietin in the gastric juice (3, 2).

These findings suggest a further, as yet unknown, link in the normal relationship between the bone-marrow and the active principle which is stored in the liver—in the case of achrestic anaemia the absence of this link is the determining factor, since we have shown that the ability to store the principle is not impaired.

The ability of the liver to store the antipernicious anaemia principle may in fact be lost in patients with cirrhosis of the liver, and although free hydrochloric acid is often present, a blood picture resembling that seen in pernicious anaemia will result. Wintrobe and Shumacker (9), van Duyn (5), and van den Bergh, Hijmans, and Kamerling (4) in describing the occurrence of megalocytic anaemia in association with hepatic disorders showed that there was no difficulty in differentiating these cases, and they drew attention to the feature of spontaneous remission of the anaemia occurring, in spite of clinical aggravation of symptoms. Such has not been seen in achrestic anaemia (2). The anaemia of patients with hepatic disease will often respond to liver therapy (9, 1, 10), although this is not always the case.

The probability of other as yet unidentified steps and mechanisms in the process of normal erythropoiesis has become more obvious. The manner in which the liver principle is mobilized from the liver and utilized in the further elaboration of the red cells is quite unknown, and there is no reason to assume that impairment of this stage is due entirely to toxic causes—there is some evidence to suggest that some of these cases may be the result of other deficiencies.

Summary

1. Investigations into the presence of the antipernicious anaemia principle in the livers of patients suffering from anaemias have been continued and compared with normal human and calf liver.

2. Further fractions have been prepared for parenteral administration from the livers of cases of achrestic and aplastic anaemias and subjected to examination for their antipernicious anaemia activities.

3. The antipernicious anaemia activities of the fractions have been determined by direct clinical trial on cases of relapsing pernicious anaemia under carefully controlled conditions as previously described.

4. The liver antipernicious anaemia principle was shown to be present in the livers from patients suffering from achrestic anaemia, and from aplastic anaemia in amounts at least equal to those found in normal human or calf livers.

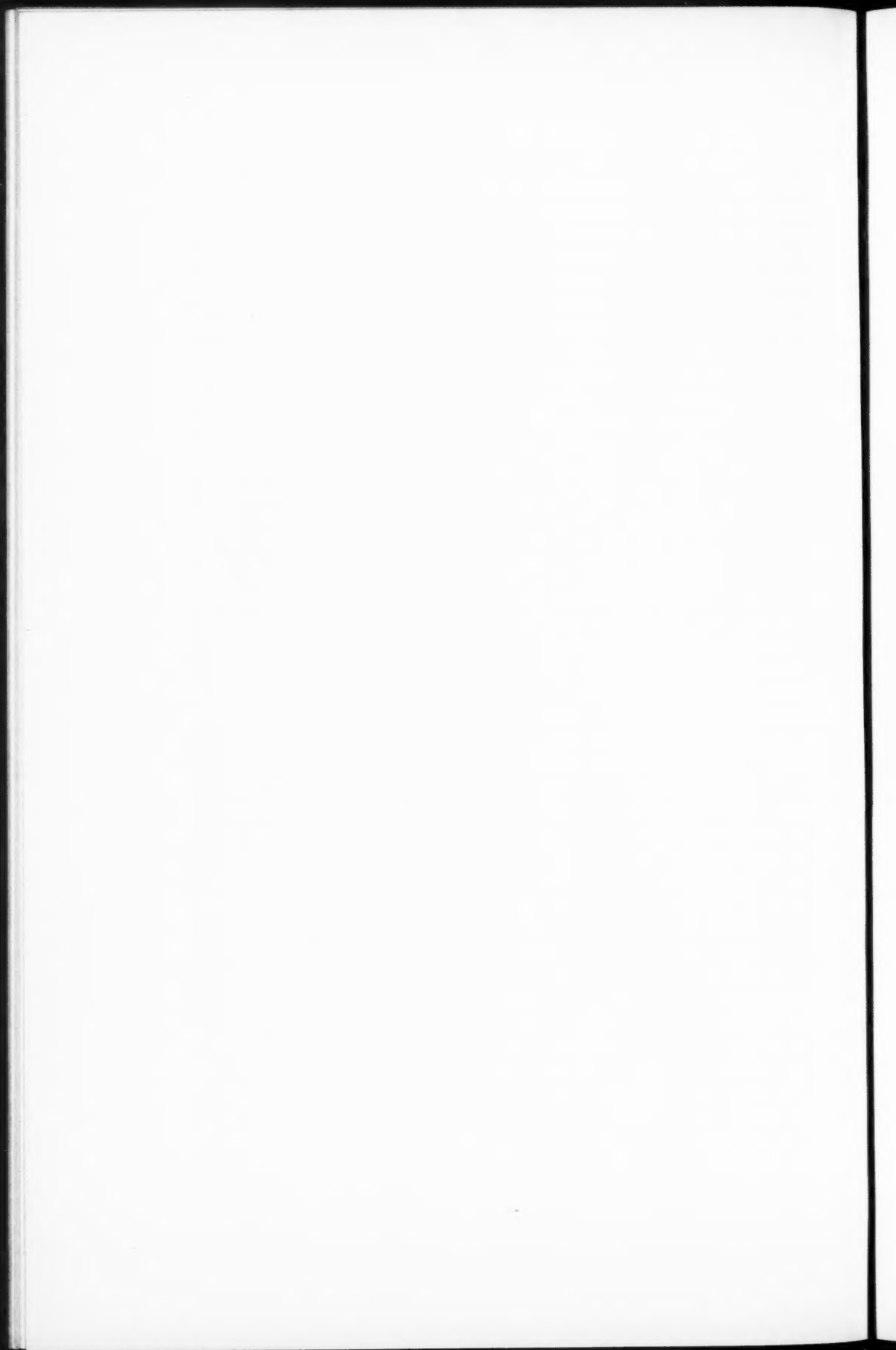
5. Opportunity was afforded for confirming the absence of the liver antipernicious anaemia principle from the liver of a case of fatal untreated pernicious anaemia dying from pulmonary embolus.

6. These findings have been discussed in their relationship to the aetiology of anaemias.

This work has been carried out with the aid of grants from the Medical Research Council.

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OBSERVATIONS ON THE SITE OF THE ANTAGONISTIC
ACTION OF POSTERIOR PITUITARY EXTRACTS ON
INSULIN HYPOGLYCAEMIA¹

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Introduction

THE effect of extracts of the posterior lobe of the pituitary gland in preventing the hypoglycaemia following insulin injections was demonstrated by Burn (1), who summarized his results by stating that 'subcutaneous injections of extract of posterior lobe of the pituitary gland given simultaneously with injection of insulin diminish or abolish the fall of blood-sugar produced by the latter. *The doses of pituitary extract used do not, when given alone, produce a rise of blood-sugar sufficient to explain this inhibition of the action of insulin as being the result of an algebraic sum.*'

The site of action of this antagonism and its mode of production remained uncertain. It has been suggested that posterior pituitary extract causes glycogenolysis, probably through the intermediate action of adrenalin. Clark (2) concludes from experiments on cats, in which the liver had been cut out of the circulation, that the source of glycogen in pituitary hyperglycaemia is the liver. Fritz (3) reports that the hyperglycaemic effect does not occur in suprarenalectomized animals. Lawrence and Hewlet (4) have stated that ergotamine, which paralyses the sympathetic, will also inhibit pituitary hyperglycaemia and the antagonism between insulin and posterior pituitary extract. Nitzescu (5) denies this ergotamine action, and working with Benetato (6) showed that pituitrin produces an increase in the glycogen content of the liver, which may amount to 2 per cent., whilst the muscle glycogen was found to be diminished. Stenström (7), Burn (1) and others have shown that posterior pituitary extract will also antagonize the hyperglycaemic effects of adrenalin. It is unlikely that posterior pituitary extract would antagonize insulin by causing a secretion of adrenalin, which is itself antagonized by the action of posterior lobe extract.

It was decided to reinvestigate certain aspects of this problem anew, especially with regard to the possible site of the antagonism between posterior pituitary extract and insulin. In an earlier paper (8) we recorded the effects of injections of infundin (the posterior pituitary extract prepared by B. W. & Co.) on the blood-sugar of man (a) when given alone, and (b) when administered combined with oral glucose. The results of these experiments

¹ Received January 20, 1937.

may be summarized thus: (i) subcutaneous injections of *therapeutic doses* of infundin have no appreciable influence on the blood-sugar; (ii) subcutaneous injections of the same small doses of infundin, combined with the administration of glucose, will produce a more marked and prolonged hyperglycaemia than that produced by glucose alone. Our results confirm those of Burn (1), and Lawrence and Hewlet (4) in giving no indication of the direct mobilization of glucose by infundin. Considered in the light of the observations of Zunz and La Barre (9)—that hyperglycaemia is itself an adequate stimulus for the secretion of insulin—our findings would suggest that infundin antagonizes the insulin secreted in response to this hyperglycaemia, thus enhancing the level of the blood-sugar.

Foster (10) has shown that after administration of glucose the capillary blood-sugar curve rises higher than the venous blood-sugar curve (*a-v* difference). Correlation of the results of various investigators establishes that this *a-v* difference is due to the action of insulin in the peripheral tissues. Mann and Magath (11), and Burn and Dale (12) demonstrated the peripheral action of insulin. Frank, Nothmann, and Wagner (13) in experiments on normal and depancreatized dogs, have shown that injection of insulin causes an increase of the *a-v* difference, whilst Lawrence (14), and Rabinowitch and Bazin (15) have demonstrated a diminished *a-v* difference in diabetes, and its increase under the action of insulin. These observations suggest that the difference between the sugar-content of arterial and venous blood at any particular time is an indication of the insulin then present in the tissues. A study of the *a-v* differences after administering glucose and injecting infundin should therefore determine the effect of the latter on the insulin normally secreted in response to a rising blood-sugar.

In the following series of experiments these *a-v* differences were determined in the healthy adult male after the combined administration of glucose orally and infundin parenterally.

Experimental

(i) *Procedure.* These experiments were undertaken on a group of healthy medical students and hospital patients (non-diabetic). 50 grm. of glucose in 100 c.c. water, flavoured with tr. aurantii, was administered, and simultaneous samples of venous and capillary blood were withdrawn every 20 minutes for a two-hour period. Venous blood was collected from the median basilic vein, using a small all-glass syringe and hypodermic needle, $\frac{1}{2}$ c.c. being withdrawn on each occasion as only 0.2 c.c. is necessary for the estimation of glucose. Capillary blood was obtained from the finger tip, the blood being rapidly collected into a small porcelain crucible which had previously been coated with a film of fine oxalate crystals. Foster (10) has shown that arterial blood has the same sugar content as capillary blood. The samples were analysed for glucose, using the Folin-Wu technique. A few days later the procedure was repeated, with the addition this time of an injection of $\frac{1}{2}$ c.c. infundin. The injection was given immediately following the administration of the glucose in the majority of cases, whilst in a few it

was given 10 minutes or 20 minutes later. 'Pitressin' (Parke, Davis & Co.) was used instead of infundin in a few cases.

(ii) *Results.* Administration of glucose produced the usual increase in blood-sugar in all cases; the *a-v* differences were observed, the most marked difference being noted at the height of the hyperglycaemia.

TABLE I

Cases Showing Marked Enhancement of the Blood-sugar Level (over 45 mg. per cent.) after the Combined Administration of Glucose and Infundin or Pitressin.

Case.	Experiment.	Blood-sugar (mg. %) (Minutes after glucose).							
		0	20	40	60	80	100	120	140
J. C.	(i) 50 grm. glucose	Capillary blood	97	162	214	214	200	162	140
		Venous blood	93	133	167	174	162	130	130
		<i>a-v</i> difference	+4	+29	+47	+30	+38	+32	+10
	(ii) 50 grm. glucose + $\frac{1}{2}$ c.c. infundin	Capillary blood	88	214	279	304	214	171	136
		Venous blood	87	222	272	277	194	150	125
		<i>a-v</i> difference	+1	-8	+7	+27	+20	+21	+11
A. D.	(i) 50 grm. glucose	Capillary blood	120	143	146	167	140	91	65
		Venous blood	120	150	136	140	128	82	60
		<i>a-v</i> difference	0	-7	+10	+27	+12	+11	+5
	(ii) 50 grm. glucose + $\frac{1}{2}$ c.c. pitressin	Capillary blood	88	154	256	324	293	222	143
		Venous blood	87	150	254	332	265	214	128
		<i>a-v</i> difference	+1	+4	+2	-8	+28	+8	+15
J. M.	(i) 50 grm. glucose	Capillary blood	95	130	113	115	103	98	87
		Venous blood	91	117	95	103	102	91	80
		<i>a-v</i> difference	+4	+13	+18	+12	+1	+7	+7
	(ii) 50 grm. glucose + $\frac{1}{2}$ c.c. pitressin	Capillary blood	102	100	133	200	188	128	103
		Venous blood	97	97	133	194	167	117	100
		<i>a-v</i> difference	+5	+3	0	+6	+21	+11	+3
G. E.	(i) 50 grm. glucose	Capillary blood	88	146	158	150	154	146	113
		Venous blood	92	130	136	125	133	113	94
		<i>a-v</i> difference	-4	+16	+22	+25	+21	+33	+19
	(ii) 50 grm. glucose + $\frac{1}{2}$ c.c. infundin	Capillary blood	92	123	200	210	196	162	128
		Venous blood	89	120	193	195	182	150	115
		<i>a-v</i> difference	+3	+3	+7	+15	+14	+12	+13
M. F.	(i) 50 grm. glucose	Capillary blood	100	158	200	125	115	125	100
		Venous blood	89	143	158	89	95	103	88
		<i>a-v</i> difference	+11	+15	+42	+36	+20	+22	+12
	(ii) 50 grm. glucose + $\frac{1}{2}$ c.c. infundin	Capillary blood	103	146	210	246	214	187	125
		Venous blood	91	136	178	214	184	160	107
		<i>a-v</i> difference	+12	+10	+32	+32	+30	+27	+18

After the combined administration of glucose and infundin or pitressin, the majority of cases showed an enhanced hyperglycaemia. The degree of this increase in the hyperglycaemic level varied, however, in different individuals, the range being from 7 to 157 mg. per cent. increase over the original hyperglycaemia produced by glucose alone.

In analysing these results we have divided the cases into two groups: (1) those showing a marked enhancement of the blood-sugar level (over 45 mg. per cent.) after combined glucose and infundin; and (2) those showing an enhanced hyperglycaemia of less than 45 mg. per cent.

The cases in group (1) are recorded in Table I, and representative cases from this group are shown graphically in Fig. 1. It will be noted that there is a marked diminution in the *a-v* differences as compared with the control *a-v* differences, and that the higher the hyperglycaemia the more striking is this diminution in the *a-v* difference. This is also most marked whilst

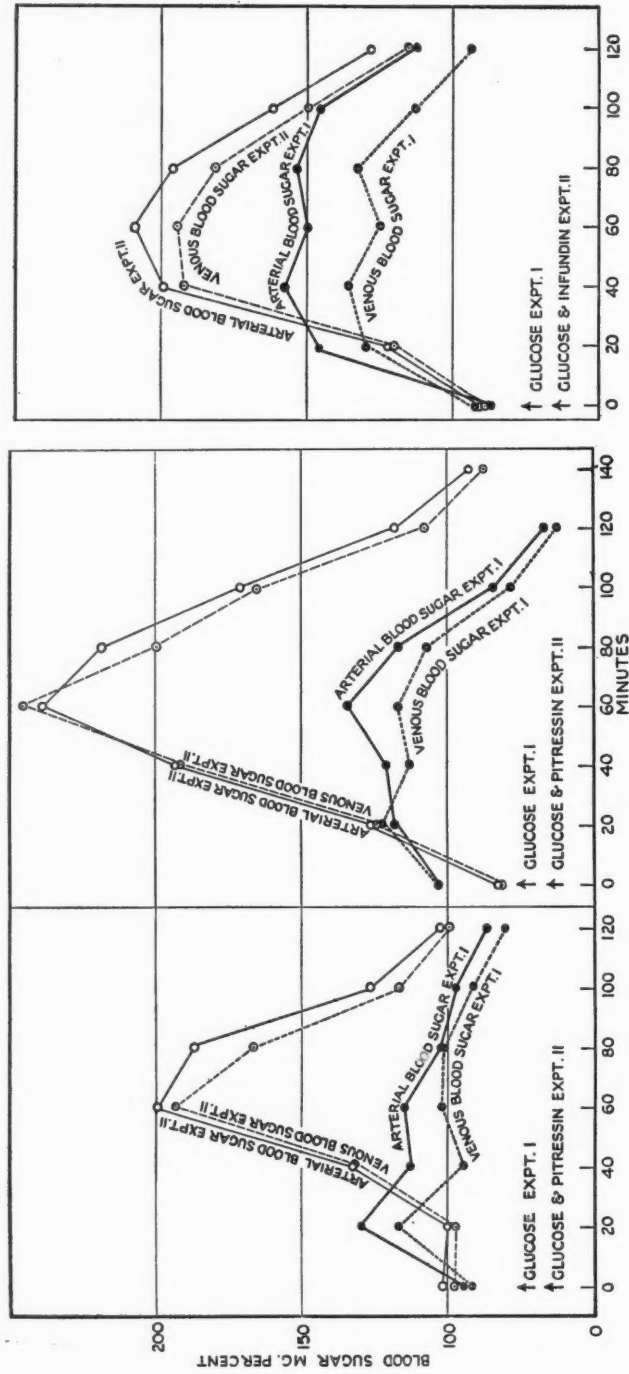


FIG. 1. Showing the effect on the arterial and venous blood-sugar of:—

(1) 50 gm. glucose orally.

(2) 50 gm. glucose orally combined with subcutaneous injection of 1/2 c.c. infundin or pitressin.

the blood-sugar is rising; as the blood-sugar level falls, the *a-v* differences begin to increase and soon reach a degree comparable with the normal.

Group (2) cases (shown in Table II) show but slight variations in *a-v* differences after glucose alone and glucose combined with infundin. Fig. 2 shows one of these cases.

TABLE II

Cases Showing Enhancement of the Blood-sugar Level of Less than 45 mg. per cent. after the Combined Administration of Glucose and Infundin.

Case.	Experiment.	Blood-sugar (mg. %) (Minutes after glucose)							
		0	20	40	60	80	100	120	150
A. S.	(i) 50 grm. glucose	Capillary blood	97	150	158	125	109	107	97
		Venous blood	88	125	133	105	85	91	86
		<i>a-v</i> difference	+9	+25	+25	+20	+24	+16	+11
	(ii) 50 grm. glucose + ½ c.c. infundin	Capillary blood	86	89	111	162	174	140	146
		Venous blood	82	89	98	140	136	107	109
		<i>a-v</i> difference	+4	0	+13	+22	+38	+33	+35
H. E.	(i) 50 grm. glucose	Capillary blood	87	94	150	162	150	120	105
		Venous blood	85	94	136	140	125	105	102
		<i>a-v</i> difference	+2	0	+14	+22	+25	+15	+3
	(ii) 50 grm. glucose + ½ c.c. infundin	Capillary blood	95	105	130	150	158	140	117
		Venous blood	87	107	120	140	136	115	97
		<i>a-v</i> difference	+8	-2	+10	+10	+22	+25	+20
B. M.	(i) 50 grm. glucose	Capillary blood	95	130	167	143	130	136	128
		Venous blood	91	136	140	130	105	107	91
		<i>a-v</i> difference	+4	-6	+27	+13	+25	+29	+29
	(ii) 50 grm. glucose + ½ c.c. infundin	Capillary blood	92	105	123	150	174	140	125
		Venous blood	87	107	115	150	158	117	97
		<i>a-v</i> difference	+5	-2	+8	0	+16	+23	+28
S. H.	(i) 50 grm. glucose	Capillary blood	115	133	150	140	143	120	97
		Venous blood	111	125	130	128	133	95	89
		<i>a-v</i> difference	+4	+8	+20	+12	+10	+25	+8
	(ii) 50 grm. glucose + ½ c.c. infundin 10 mins. after glucose	Capillary blood	94	123	133	158	171	140	107
		Venous blood	86	125	123	150	154	102	97
		<i>a-v</i> difference	+8	-2	+10	+8	+17	+38	+10
N. R.	(i) 50 grm. glucose	Capillary blood	85	167	222	214	158	91	89
		Venous blood	82	140	181	171	103	83	77
		<i>a-v</i> difference	+3	+27	+41	+33	+55	+8	+12
	(ii) 50 grm. glucose + ½ c.c. infundin 20 mins, after glucose	Capillary blood	87	171	188	207	194	133	94
		Venous blood	87	154	162	181	154	88	74
		<i>a-v</i> difference	0	+17	+26	+26	+40	+45	+20
B. B.	(i) 50 grm. glucose	Capillary blood	85	162	174	167	125	130	103
		Venous blood	86	143	154	154	125	128	100
		<i>a-v</i> difference	-1	+19	+20	+13	0	+2	+3
	(ii) 50 grm. glucose + ½ c.c. infundin 20 mins. after glucose	Capillary blood	95	167	171	207	162	143	125
		Venous blood	95	127	154	188	150	146	115
		<i>a-v</i> difference	0	+40	+17	+19	+12	-3	+10

Another fact which emerges from these results is that the peak blood-sugar, after glucose combined with infundin, often occurs 20-40 minutes later than that produced by glucose alone. This is possibly due to the fact that infundin decreases the rate of absorption of glucose from the gastro-intestinal tract (Thiernes and Hockett (16)).

The results thus demonstrate that *if in the same individual the combined administration of infundin and glucose gives a much higher glycaemia than that following glucose alone, the a-v difference of the former is small compared with the latter; if the infundin produces little alteration in the glycaemic curve, the a-v difference shows but little change.*

Discussion

Experimental evidence has been quoted showing that the *a-v* difference is an index of the insulin activity at any particular time. Our results show that this *a-v* difference is diminished during the ascent of the hyperglycaemia after the administration of glucose and infundin. This suggests that infundin causes an inhibition of the primary effect of the insulin which is normally secreted in response to oral glucose administration, and because

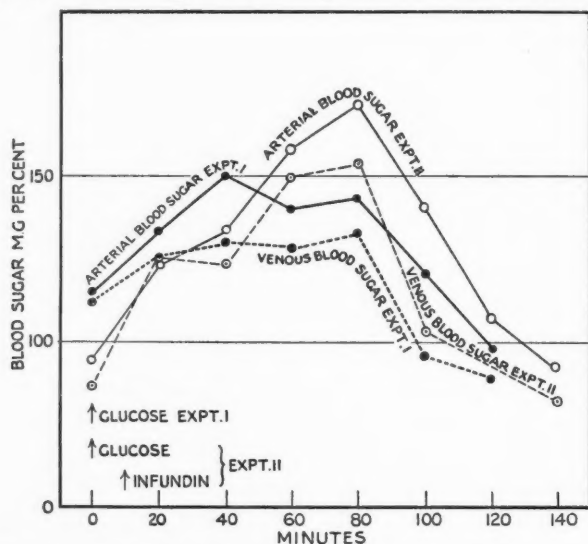


FIG. 2. Showing the effect on the arterial and venous blood-sugar of:—
 (1) 50 grm. glucose orally (Expt. 1).
 (2) 50 grm. glucose orally combined with subcutaneous injection of $\frac{1}{2}$ c.c. infundin 10 minutes later (Expt. 2).

of this an enhanced hyperglycaemia occurs. When the infundin action has ceased, insulin begins to exert its action, the blood-sugar falls and the *a-v* differences now become more marked and approach the values seen after oral glucose. Further evidence of this action is afforded by the fact that those cases in which the *a-v* differences showed the most marked diminution also showed the greatest degree of hyperglycaemia, i.e. the most marked inhibition of insulin occurred in these cases. When the infundin action did not produce any notable effect on the hyperglycaemia after oral glucose, the *a-v* differences were of the same magnitude as in the control, suggesting that insulin was not inhibited to the same extent.

The possibility of mobilization of muscle glycogen is another factor which must be considered. That such mobilization, however, does not cause hyperglycaemia, is shown by the work of Fletcher and Hopkins (17) who demonstrated that mobilization of muscle glycogen causes an increase of blood lactic acid and not an hyperglycaemia, the lactic acid passing to the liver where it is eventually transformed to glycogen.

Summary

1. The *a-v* differences in blood-sugar have been investigated (a) after the administration of glucose, and (b) after the combined administration of glucose and posterior pituitary extract.

2. The combined administration of glucose and infundin produces a more marked and prolonged rise in the blood-sugar than that following an equivalent amount of glucose orally.

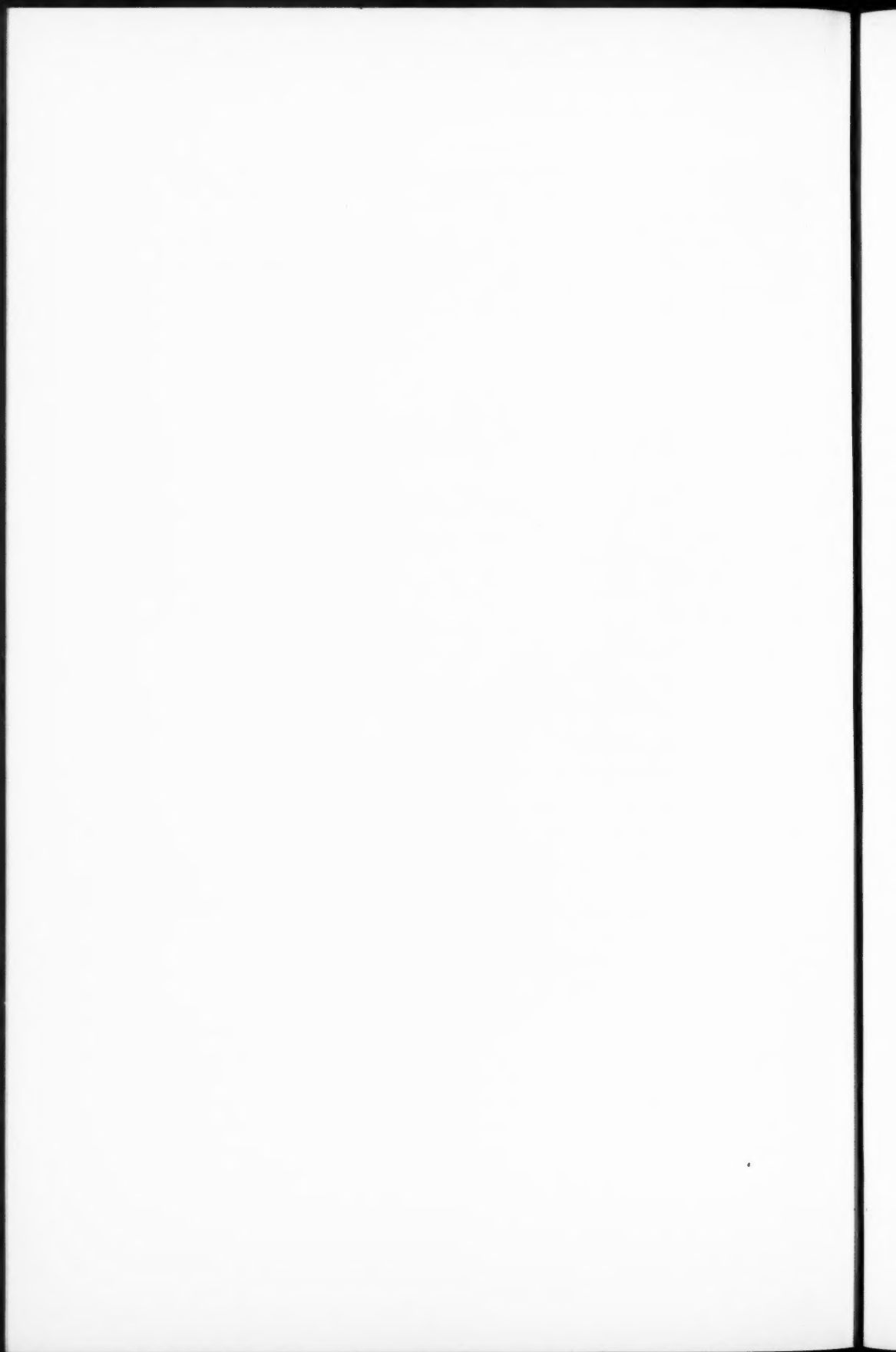
3. When the effect of infundin on the glucose tolerance curve is marked the *a-v* differences are diminished.

Conclusion

Posterior pituitary extracts antagonize insulin hypoglycaemia by retarding the *peripheral* utilization of the blood-sugar.

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OBSERVATIONS ON SKIN SENSITIVITY IN ASTHMATIC
AND CONTROL SUBJECTS¹

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SINCE MOSS (20) first suggested the intradermal injection of horse serum as a means of detecting serum-sensitive subjects, skin testing has been extensively employed as an index of sensitivity to atopic² substances. The conclusions which may legitimately be drawn from the development of a reaction, or the absence of such a reaction, are, however, still based on opinion rather than knowledge of fact. The shortcomings of the test are too infrequently recognized. This is, to a great extent, because there is little information on the frequency of reactions in healthy subjects. Such information is essential not only in estimating the practical value of skin tests, but also in forming a true conception of the part played by the presence of sensitivity in the production of asthma and allied conditions. It was to obtain information of this kind that the present work was undertaken.

In the past, attention has mainly been directed to the frequency of specific skin reactions in subjects giving a history of symptoms, clearly produced by exposure to certain foods or inhalants. The relative merits of the intradermal and the scratch methods of performing the tests have also been much discussed. Later workers have on the whole favoured the former method as being the more accurate and sensitive (5), (4), (6), (15), (22), (25)). This conclusion is reached mainly on the ground that in cases where sensitivity to a certain substance is recognized from the patient's history, it can be confirmed more frequently by this method than by the scratch test. This applies not only to asthma but to other atopic states. The difference between the two methods is, however, merely one of degree as Fineman (13) has clearly shown. The intradermal test has been used in the present study.

It is well recognized by Coca (7), and by Rackeman (23) that neither the scratch nor the intradermal test offers entirely reliable information as to whether symptoms will or will not develop when the test substance is brought into contact with the tissues of sensitized subjects under natural conditions. Positive skin reactions are often obtained, which cannot be

¹ Received January 5, 1937.

² 'Atopy' and its adjective are used throughout this paper rather than 'Allergy'. The latter term, by von Pirquet's own definition includes such a wide range of conditions and has been used with so many different meanings by various authors, that it has been thought wise to avoid it entirely. 'Atopy', a term invented by Coca still retains a definite and limited meaning.

confirmed by other means, particularly when the intradermal test is used. Conversely, there may be complete failure to reveal a sensitivity which is recognized in the history and confirmed by trial, particularly when the scratch test is employed. As a corollary to this Fineman (13) has shown that there is no direct relationship between the severity of symptoms in pollen sensitive asthmatics and the degree of sensitivity to intradermal (or conjunctival) tests. It is therefore clear that there is no precise or direct relationship between the results of skin tests and the behaviour of the tested subject, when he is exposed naturally to those foods or inhalants which give positive responses.

Until recently the presence of a positive skin reaction has been tacitly accepted by many as an indication of the presence of an underlying sensitivity of practical importance to the patient. This view has been widely held in spite of the fact that discrepancies such as those already referred to are well known. The observations that follow will show upon what a false foundation this belief rests.

Intradermal tests have been carried out under the same conditions on a series of control subjects and of asthmatics.

Extracts of five different substances have been employed, two inhalants, horse dander and chicken feathers; two foods, wheat and egg white. These are generally recognized to be among the commonest causes of sensitization among asthmatic subjects for substances obtaining entry to the body through the lungs or alimentary tract respectively (Alexander (1)). Dilutions of pure horse serum albumin (kindly supplied by Sir Henry Dale, Medical Research Inst., Hampstead), were also included as a control since contact with this substance is relatively uncommon.

Methods of Preparation and Standardization of Extracts.

The extracts were prepared as follows: In the case of horse dander and feathers, extraction was carried out for from two to five days at room temperature with Evans's (12) buffered phosphate solution containing 0.5 per cent. phenol, as recommended by Coca. The wheat used was the whole grain roughly ground in a milling apparatus and similarly extracted. The egg albumin was diluted directly with Evans's solution and the serum albumin was weighed out in crystalline form and dissolved in the required volume of fluid. All the extracts were filtered through a Seitz filter, and cultured on agar slopes to exclude infection. A supply of concentrated extract was kept in a refrigerator and fresh dilutions were made from time to time during the course of the investigations. Entirely fresh extracts were made up every few months so that the results obtained should not be based upon injections made from dilutions of a single extract, and in order to avoid possible diminution in strength of the extracts with the passage of time. The extracts were kept in rubber-capped bottles. Most of the workers recommend washing the materials to be extracted with alcohol or ether, for the purpose of removing grease, before extraction is begun. This was not done in the present observation, in order that the extracts of these materials should be obtained in as natural a state as possible.

An obvious source of discrepancy enters into investigations dealing with extracts of most natural substances, namely, that one is not dealing with pure compounds of known composition. Until more is known of the chemistry of the reactive agents, it is impossible to standardize accurately extracts of such substances as horse dander, feathers, or wheat. Variations in potency of extracts prepared by different methods, and from different samples of material, are bound to occur as long as this lack of knowledge exists and must be freely admitted. Two rough methods of standardization have been employed in the past: (1) By adding a known amount of extracting fluid to a weighed amount of the material to be extracted, and carrying out the extraction under standard conditions, and (2) By determining the nitrogen content of the extract. The latter method is recommended by Rackemann (22), and Coca (7), and was thought to be the most suitable for the present work.

The horse dander extracts made at different times were found to be remarkably constant in activity when comparable strengths were used, but different extracts of feathers and wheat showed considerable variations. Coca refers to the difficulty of extracting the active principle from feathers, and regards differences in the quality of the extracts used for testing as responsible for the wide variations in the published figures. A number of experiments were carried out in the course of the present work to discover a reason for these variations in potency, but with incomplete success. It seemed, however, that a prolonged extraction of feathers (e.g. five days) yielded a more potent extract for a given nitrogen concentration than a short one (e.g. two days). Washing with ether and previous autoclaving appeared to cause a diminution in potency, and it was suspected that extraction at 21°C. yielded a more potent extract than at 15°C. We were unable to find any satisfactory explanation for variations in the potency of wheat extracts. It is possible that infection with mites, as reported by Van Leeuwen (16), accounted for the frequency with which reactions were obtained from certain samples. For comparative purposes, the variability does not matter so long as a roughly equivalent number of control and asthmatic subjects are tested at the same time and with dilutions of the same extracts. This was in fact done. Throughout, extracts of good potency were employed rather than weaker samples. The extracts were employed in three different strengths, containing 20, 2, 0.2 mg. per cent. of nitrogen.

Method of testing and recording results. A separate all-glass syringe was kept for each set of extracts. These were graduated in hundredths of a cubic centimetre. Care was taken to avoid carrying over small quantities of the stronger solutions into the weaker concentrations by passing from one strength, only to the next above or below it. In this way the syringe would never be taken out of the strongest solution (20 mg. per cent.) and passed directly into the weakest (0.2 mg. per cent.).

The syringes were frequently washed out in Evans's solution. It was thought, however, owing to the high percentage of reactions obtained with the weakest solutions, that even with these precautions, traces of the more concentrated extracts might be carried down to the weaker dilutions. A group was therefore tested using a fresh syringe whenever the weakest extract was withdrawn, and the series of injections was made in ascending order only. It was found that this did not alter the percentage of reactions obtained. Thus, of fifty-five asthmatic subjects tested with ascending strengths of horse dander extract, 47 per cent. reacted to the weakest dilution (0.2 mg. nitrogen per cent.), compared with 47 per cent. and 38 per

cent. for the preceding 50 and 60 cases respectively, tested in the original way.

A quantity of 0.02 c.c. of extract was injected intradermally for each test. In the event of a positive reaction the diameter of the wheal formed was roughly measured when the reaction was judged to be at its height. The difference between the diameter of this wheal and that of the original bleb formed by the injection of the test material was recorded. For the purpose of measuring wheals, pseudopodial outgrowths were disregarded. The diameter of any flare which might develop was also measured, after sufficient time had been allowed for the transient flare sometimes arising as the result of the trauma of the injection to subside. A positive reaction was taken to be shown by the presence of a wheal and flare or of a flare only. Many workers have demanded the presence of both wheal and flare before regarding a reaction as positive (Baker (2), Longcope (19), Schloss (29)) and in some cases have gone so far as to fix an arbitrary minimal size for the wheal (Walker (31)). There is no justification for this on theoretical grounds, since in a sensitive subject, it is always possible by diluting the extract, to obtain a reaction consisting of just this reflex flare, measuring from 15-30 mm. in diameter unaccompanied by any increase in the size of the original wheal. The same effect can be demonstrated with dilutions of histamine. It follows that a flare alone, must be regarded as differing merely in degree from the more fully developed triple response. As such it indicates in the presence of a negative control test a slight degree of skin sensitivity, and cannot therefore be ignored. For the sake of completeness, however, figures given in brackets (Tables I and III) indicate the percentage of reactions represented by the presence of flare only.

Four of the asthmatic subjects in the present series gave reactions to all forms of intracutaneous injections, including those of normal saline. In these cases no reactions have been recorded in the tables of this paper unless they have been clearly larger than the control response.

Composition of the Asthmatic Group

These cases consisted of unselected patients attending the Asthma Clinic at Guy's Hospital, and were all tested at their first or second attendance before commencing treatment. Very few had previously been tested for evidence of skin sensitivity. A few had had vaccine treatment or injections of a non-specific character elsewhere before attending at the clinic. Later a number of children over three years of age attending the Asthma Clinic at The Hospital for Sick Children, Great Ormond Street, were included. These were having medicinal treatment only. The first 110 cases of asthma were tested with all five test substances. The children and the adults who were added later, were tested with one or two extracts only. Of these there were 293.

Composition of the Control Group

This was composed of medical students and patients from the wards of Guy's Hospital or attending the Out-Patient Department of that hospital or the Hospital for Sick Children, Great Ormond Street. One hundred of these,

TABLE I
Relative Sensitivity of Asthmatic and Control Groups to Various Extracts.

	Horse dander.			Chicken feathers.			Wheat.			Egg white.			Horse serum albumin.		
	No. of subjects tested.	20 mg. nit. %	2 mg. %	No. of subjects tested.	20 mg. nit. %	2 mg. %	No. of subjects tested.	20 mg. nit. %	2 mg. %	No. of subjects tested.	20 mg. nit. %	2 mg. %	No. of subjects tested.	20 mg. nit. %	2 mg. %
Asthmatics	148	75 (7)	60 (12)	39 (12)	33 (9)	51 (8)	179 (11)	47 (11)	27 (11)	19 (6)	12 (3)	9 (1)	114 (8)	18 (8)	8 (4)
Controls A	190	37 (15)	12 (4)	3 (5)	2 (7)	15 (6)	62 (11)	23 (11)	3 (1)	103 (6)	0 (0)	0 (0)	62 (3)	10 (3)	2 (0)
Controls B	97	50 (8)	34 (5)	17 (3)	9 (9)	27 (6)	37 (8)	40 (8)	22 (5)	52 (6)	0 (0)	0 (0)	37 (5)	11 (5)	5 (2)

The figures showing the number of reactions are in percentages.

mostly between the ages of fifteen and thirty years, were tested with all five extracts, while 242 were tested with one or two extracts only. Each subject was questioned as to the presence of any condition of possibly atopic origin, which had ever been present in himself or any member of his family. Conditions specifically referred to included asthma, eczema, rhinorrhoea, hay-fever, urticaria (including 'heat bumps' and 'nettle rash') or migraine. The control subjects were subdivided into two groups A, those in whom or in whose families there was no evidence of an atopic state at any time, and B, those in whom such a history was actually obtained. No case was included in either group who was known to have suffered from asthma, eczema, hay-fever, or rhinorrhoea within three years of being tested, but those who had had occasional migraine or isolated attacks of urticaria (mainly children with papular urticaria) within that period were included in Group B. The latter contained 115 subjects, compared with 227 in Group A.

The results of the tests are briefly summarized in Table I, which shows the percentage number of reactions to each extract in the asthmatic group and Control Groups A and B for the five test substances.

All figures are in percentage unless specified. Those in brackets refer to reactions consisting of a reflex flare only. The figure above these indicates the total percentage of reaction obtained, i.e. those with flare only or flare and wheal.

It can be seen that sensitivity to horse dander, chicken feathers, and wheat is very common in the asthmatic group, and though infrequently shown by the weaker dilutions, occurs in one-quarter to one-third of the subjects composing Control Group A, when strong testing solutions are employed. Group B occupies an intermediate position. Extracts of those substances which are most potent in producing positive reactions among asthmatics also give rise to the greatest number of reactions in the control groups.

Comparison of the size of the reactions in the different groups shows that large wheals are produced far more commonly in the asthmatic, than in the control groups. The position occupied by Group B is also in this respect intermediate between the Asthmatic Group and Group A. Table II shows the frequency with which responses of different sizes were observed in subjects between fifteen and thirty years of age, tested with horse-dander extract. Similar results were obtained with other test substances and for the other age groups.

It is evident that large wheals with pseudopodial outgrowths occur commonly in asthmatics, and only rarely among subjects in the Control Group A. The number of slight reactions indicated by reflex erythema only is proportionally far greater in this latter group, than in the asthmatic group or Group B. At the same time the presence of individuals giving large responses in Group B proves that a high degree of skin-sensitivity in any particular subject is not necessarily accompanied by the symptoms of an atopic state.

Relationship between Naturally Occurring Sensitivity and Sensitivity shown by Skin Tests

It is evident from what has been said that sensitivity may often be demonstrated by means of the intradermal skin test, when it is not shown in any other way. Clearly, this was always so in the Control Groups A and B: in the asthmatic subjects confirmation of the sensitivity to horse

TABLE II

Distribution of Reactions to Horse Dander According to Size Among Groups of Control Subjects and Asthmatics.

	No. of cases.	Group A.			No. of cases.	Group B.			No. of cases.	Asthmatic Group.		
		20 mg. nit. %.	2 mg. nit. %.	0.2 mg. nit. %.		20 mg. nit. %.	2 mg. nit. %.	0.2 mg. nit. %.		20 mg. nit. %.	2 mg. nit. %.	0.2 mg. nit. %.
	72				54				49			
Flare only		10	4	0		4	2	2		4	4	9
Flare and increase of wheal diameter of less than 6 mm.		17	7	2		23	20	12		24	23	15
Flare and wheal with presence of pseudopodia or increase of diameter of 6 mm. or more		0	0	0		9	4	0		16	11	9

Figures are given in actual numbers.

hair, feathers, and wheat was only obtained from the history in occasional cases. There is little doubt, however, that contact with material giving positive skin reactions leads to the development of symptoms more often than a confirmatory history would lead one to suppose, as subsequent trial contact or avoidance of suspected substances may show, since many patients are unobservant in these matters. Definite evidence of sensitization to one of these substances, based on the patient's personal experience was always confirmed by the skin test in this series. The majority of these subjects with recognized sensitivity to one of the test substances gave large reactions with pseudopodial wheals to the strongest, and in many cases to the middle dilution of the corresponding extract; the weakest dilution usually also gave a definite response. For example, three asthmatic subjects employed in bakeries whose asthma was definitely associated with their employment, all gave large reactions to flour in all dilutions tested. Previously recognized sensitivity to egg was common among the asthmatic children, in some of whom the eating of eggs produced intestinal symptoms or an exacerbation of their eczema; and in contrast to the inhalant substances a reaction was rarely given unless the sensitivity was confirmed by the history. In agreement with this is the fact that skin reactions to egg were rarely seen in the control groups, and such reactions as occurred were small, and produced by the highest concentration of extract only. On the other hand, a patient (not

included in the present series) in whom diarrhoea and vomiting had occurred over a number of years, whenever food containing egg had been eaten, gave completely negative results when tested with the same extracts. Responses to horse serum were also small, and with the exception of one subject in Group A who recollected having been given a therapeutic injection of horse serum some years previously, there was no relationship between the reaction obtained and previous administration of serum. Serum sensitivity is, however, generally shown by a delayed type of response, which has not been considered for the purpose of this paper.

Multiple sensitivity. It was observed that multiple sensitivity was common among those subjects who were tested with all five of the test materials. Again the asthmatic group and Group B contained a greater relative number of subjects sensitive to more than one extract than did Group A. In this last group, of the fourteen subjects who reacted to any extract in a strength of 2 mg. nitrogen per cent. or less, five reacted to one or more other substances in addition, whereas in Group B, seventeen out of nineteen showed multiple sensitivity, and in the asthmatic group twenty-nine out of thirty-two, for the same strength of extract. This tendency to show multiple sensitivity is well recognized in asthmatics (31), (18), (9), and in hay-fever subjects (10), (23).

The effect of age. The incidence of skin sensitivity in asthmatic subjects is known to vary at different ages, and it is of interest to know whether similar variations also occur among controls. In Table III the subjects are arranged in different age groups to show this. In certain groups (notably Group B) the number of subjects over the age of thirty is small and the two older age groups have therefore been combined in some instances.

The well recognized fact that in asthmatic subjects sensitivity to inhalants rises to a peak in young adult life whereas food sensitivity is most commonly seen in early childhood, is well illustrated by the figures for horse dander, chicken feathers, and egg white in this table. In the control groups it is clear that sensitivity to inhalants also occurs most commonly between the ages of fifteen and thirty years. The number of sensitive subjects in the younger and older groups drops sharply in Group B, and this variation with age, though less clearly shown is still apparent in Group A. Although some of the groups are small and statistically insignificant, the general agreement between them adds weight to the observations, especially because in the youngest control groups the tests with horse dander and chicken feathers were carried out on separate individuals.

Wheat occupies an apparently anomalous position, since as a food one would expect the highest incidence of sensitivity to be found in the youngest group, whereas it reacts throughout after the manner of the inhalants. This is, no doubt, due to the fact that it obtains access to the body both as a food and as an inhalant in the form of flour. The importance of the latter route is shown by the high incidence of sensitivity to flour among bakers (8) and the fact that asthmatic subjects sensitized to flour, presumably

TABLE III
Relationship between Age and Skin Sensitivity in Asthmatic and Control Groups.

	Horse dander.				Chicken feathers.				Wheat.				Egg white.			
	No. of subjects tested.	20 mg. nit. %	2 mg. nit. %	0.2 mg. nit. %	No. of subjects tested.	20 mg. nit. %	2 mg. nit. %	0.2 mg. nit. %	No. of subjects tested.	20 mg. nit. %	2 mg. nit. %	0.2 mg. nit. %	No. of subjects tested.	20 mg. nit. %	2 mg. nit. %	0.2 mg. nit. %
Asthmatics																
3-15 yrs.	14	93 (0)	71 (21)	43 (21)	75	71 (7)	57 (11)	40 (16)	77	44 (18)	27 (15)	13 (5)	122	24 (6)	16 (4)	12 (1)
15-30 "	49	88 (8)	76 (66)	66 (18)	61	81 (8)	63 (11)	50 (10)	40	50 (3)	35 (10)	20 (3)	40	12 (5)	8 (2)	3 (0)
30-45 "	48	70 (4)	57 (15)	23 (2)	55	63 (5)	44 (2)	28 (4)	32	66 (6)	28 (9)	13 (3)	32	16 (3)	9 (0)	9 (0)
45-70 "	37	57 (14)	38 (8)	22 (13)	39	46 (10)	28 (5)	15 (0)	30	6 (3)	13 (10)	3 (0)	30	13 (9)	3 (0)	3 (0)
Control A																
3-15 yrs.	32	34 (15)	6 (0)	0 (0)	37	13 (3)	5 (3)	3 (0)	—	—	—	—	41	0 (0)	0 (0)	0 (0)
15-30 "	72	37 (14)	14 (6)	4 (0)	78	42 (9)	24 (9)	9 (4)	50	21 (12)	4 (2)	2 (0)	50	2 (4)	0 (0)	0 (0)
30-45 "	40	50 (25)	15 (3)	8 (3)	27	18 (7)	7 (4)	0 (0)	12	25 (4)	0 (0)	0 (0)	12	8 (8)	0 (0)	0 (0)
45-70 "	46	28 (6)	9 (4)	0 (0)	29	21 (10)	10 (10)	0 (0)	—	—	—	—	—	—	—	—
Control B																
3-15 yrs	17	29 (12)	12 (6)	0 (0)	14	7 (7)	0 (0)	0 (0)	—	—	—	—	15	14 (14)	0 (0)	0 (0)
15-30 "	54	67 (8)	46 (4)	26 (4)	51	59 (10)	41 (10)	12 (2)	34	41 (9)	23 (6)	12 (3)	34	3 (3)	0 (0)	0 (0)
30-70 "	26	42 (8)	23 (8)	12 (4)	22	32 (14)	9 (0)	5 (0)	3	—	—	—	3	—	—	—

Figures referring to the frequency of reactions are all given in percentages. The figures in brackets refer to those subjects whose reaction consisted of a flare, with no increase in size of the intradermal wheal. The figures above these refer to the total percentage of cases reacting to the strength of the extract in question, including both those giving a flare only and those showing an increase in the size of the wheal as well. By subtracting the figure in brackets from that above it the percentage of those reacting with wheal and flare can be obtained.

Some of the groups are statistically insignificant but are included for the sake of completeness.

by the inhalant route, may be unaffected when it is taken by mouth, as were the three bakers in the present series. The high incidence of sensitivity to wheat among subjects suffering from a variety of atopic conditions, recorded by a number of authors (1), (3), (7), (26), (32) is probably also accounted for in this way.

Sensitivity to egg white occurs so rarely among the control subjects that it is impossible to show any correspondence between age and sensitivity, in comparison with the asthmatic group. Since food sensitivity attains its peak at about the second year of life (30), it is probable that inclusion of children less than three years old would have raised its incidence in this group. Schloss (11) has shown that sensitivity to foods can be demonstrated as a transient phase in the development of many normal children.

A possible alternative explanation for this apparent effect of age in the control subjects must be considered; it is conceivable that these differences depend on variations in the constitution of the control groups at different ages. Thus two-thirds of the Groups A and B between fifteen and thirty years of age were healthy medical students, while almost all the subjects in the older control groups were hospital patients who could not therefore be regarded as healthy, though the majority were convalescent, or suffering from minor disorders. Examination of the figures obtained from this point of view shows, however, that such an explanation cannot be held to account for the differences in results obtained. When figures for patients and students of the same age are compared in Groups A and B there is no material difference between them, and in certain instances a higher figure is obtained for the less healthy group.

Early in the course of the present investigation it became clear that among those subjects with a previous personal or family history of various atopic conditions, reactions occurred more frequently and were generally larger than among those individuals who could be more strictly regarded as 'normal'. A number of students with seasonal hay fever were originally included in the series, but the majority of these gave so many reactions to inhalants, horse dander, feather, and wheat that they were subsequently excluded. It was observed that three young adults who had had asthma in their childhood were markedly sensitive, also a number who had had one or more attacks of generalized urticaria. On the other hand, the relatively small number of reactions obtained among the children in this group is hard to understand. They differ from older subjects in Group B, however, in one respect, and this may be important. No less than eighteen out of twenty-two children with a personal history of atopic conditions were included owing to a history of attacks of what was probably papular urticaria, a condition rarely recorded among the older subjects and one moreover in which an atopic pathogenesis is still not beyond doubt: other conditions such as asthma, hay fever, or eczema were seldom reported as having affected this age group. Table IV shows the relative frequency of the various conditions recorded in the personal or family history.

TABLE IV

Distribution of Atopic Conditions in Members of Group B.

	Asthma.	Eczema.	Hay fever and rhinorrhoea.	Urticaria includ- ing papular urticaria.	Other manifesta- tions.
Conditions reported in family history	32	6	14	6	3
Conditions reported in personal history	4	5	5	31	6

Further analysis of the figures for Group B shows that subjects in whom a personal history of previous atopy was combined with a family history, were as a group apparently more sensitive than those with either a personal or family history alone. The reactions of these groups to horse dander extract are shown in Table V.

TABLE V

Percentage Sensitivity to Horse Dander Extract.

Cases.	No.	20 mg. N ₂ %.	2 mg. N ₂ %.	0.2 mg. N ₂ %.
With family history of atopy only	39	51	38	18
With personal history of previous atopy only	35	43	23	9
With combined personal and previous history	22	82	45	32

Discussion

Before discussing these results reference will be made to other observations on the frequency of skin sensitivity in control subjects.

These investigations may be divided according to the method of testing used. In 1920, Baker (2), employing the scratch test, investigated the sensitivity of a series of healthy children to various food extracts. He obtained ten positive and eleven doubtful reactions in 937 tests and concluded that the incidence of sensitivity in control cases was negligible. There is no information as to the total number of children tested. Peshkin and Rost (21) in a fuller investigation tested 502 children with food extracts and some inhalants, again using the scratch technique. Fifty-one (10 per cent.) of these children gave positive or doubtful reactions to one or more foods. The highest percentage of reactions (3.38 per cent.) was obtained with rye, the main form of cereal eaten by them.

Using the intradermal method, Sabatini (27) tested fifty subjects who were known to be suffering from asthma. He employed a series of common atopens in a single unspecified strength and obtained positive reactions in 19.2 per cent. Since the present work was first undertaken Rackemann and Simon (24) have published the results of tests with nine extracts carried out on sixty hospital patients. Thirty gave reactions to one or

more substances, twenty-one reacting to silk floss, twelve to rag weed, two to orris root, and three to wheat. The extracts were employed in the usual testing strengths, none containing more than 2 mg. of nitrogen per cent. As in the case of Sabatini's work these observations can be criticized on the ground that no special care was taken to ascertain that the test subjects were suitable controls—four of the sixty actually suffered from hay fever, and one was in addition known to be sensitive to cats. It is clearly unwise to refer to this as a series of 'normal' persons. Grow and Hermann (14) tested one hundred and fifty 'normal' individuals using thirteen extracts of foods and inhalants in single strengths. They found that 55 per cent. of these subjects gave reactions, 36.6 per cent. reacting to horse dander. The test subjects were mainly students and nurses between the ages of fifteen and thirty years. They found no difference in sensitivity between those who had previously suffered from atopic conditions and the remainder: family histories were not taken into account. This discrepancy with the present observations cannot be explained, but the number of subjects with a history of atopy was limited to forty and included some with dyspeptic symptoms, whose atopic origin appears to be doubtful. Salen and Dannfelt (28) whose work will be referred to again later, also found that the presence of a family history of such states did not affect the incidence of sensitivity. The main criticism of the work of Grow and Hermann is that extracts were employed in strengths varying from 4 to 10 mg. nitrogen per cent., compared with the usual testing strength of 2 mg. nitrogen per cent. The figures obtained are therefore not comparable with the majority of figures published referring to the sensitivity of asthmatics.

Other criticisms which apply equally to all these observations are that age has not been taken into consideration and that direct comparison has not been made at the same time with asthmatics or subjects suffering from some other atopic condition.

These authors are, however, in general agreement with the main finding of this paper, namely, that a number of individuals entirely free from symptoms attributable to the presence of sensitization, show skin sensitivity to the extracts of a number of common inhalants, when tested by the intradermal method. The frequency with which these reactions are obtained is here shown to be further dependent on the strength of the testing material employed, and the age of the subject. The apparent effect of age upon sensitivity is important, in so far as it shows that a diminution in specific skin sensitivity takes place over the age of about thirty. This may indicate that a spontaneous process of gradual desensitization takes place.

The frequency with which multiple sensitivity is observed suggests that these subjects differ from those who fail to react in the ease with which they have become sensitive to common sensitizing agents encountered in normal amounts, rather than owing to peculiar environmental factors exposing them to isolated atopens in high concentration. That the latter

factor is important, however, is shown by the work of Colmes, Guild, and Rackemann (8) who tested thirty-two bakers with a variety of grain extracts, and found skin reactions in fifteen of the series. None of them reported the presence of symptoms which might have been attributed to contact with these substances in their daily life. Still more recently Salen and Dannfelt (28) have carried out an important series of observations on groups of healthy subjects employed in different occupations; they show clearly that among cavalry men, and men employed in looking after animals, sensitivity to horse dander and cattle hair is higher than among bakers, who are more frequently sensitive to grain, or theatre employees, many of whom react to lycopodium.

That skin reactions occur so commonly among control subjects at first suggests that their presence in asthmatics is of little or no importance. Further consideration shows that this view cannot be held, but that our conception of the significance of sensitivity must be modified accordingly. The very much greater number of reactions obtained in the asthmatic group, particularly with the weaker strengths of extracts, and the fact that this group gives a greater number of large reactions than is found in members of the control groups, force one to conclude that there is some connexion between this evidence of sensitivity and the development of asthma. In addition to those subjects in the present series, in whom skin sensitivity was confirmed by development of asthma, when they were exposed to the test substance in the course of their daily life, there is the evidence of numerous similar cases, recorded since skin testing was first introduced, which cannot be ignored. The greater frequency with which reactions were found to occur in Group B in comparison with the more strictly normal Group A (if this is subsequently confirmed) is subsidiary evidence pointing to the same conclusion.

There can be equally little doubt, however, that in asthma and other atopic states sensitization is only one of several factors concerned in the development of symptoms. The frequency with which skin reactions to a variety of substances are found in hay fever or asthma suggests that sensitization is, as a rule, a general process affecting a number of organs and tissues. One must assume the presence of additional local factors determining the site at which the presence of sensitivity becomes manifest in the form of asthma, hay fever, or urticaria, &c. Such localizing factors are not at present recognized with certainty, but may, in some cases, consist of anatomical or physiological variations, possibly hereditary or congenital in origin, in others, changes produced by infection, or damage resulting from contact with irritant substances. Moreover, there is little doubt that symptoms arise more commonly in those tissues which come into the most intimate contact with the sensitizing substances. For example, inhalants give rise to asthma and rhinorrhoea more often than to eczema, whereas foods give rise to intestinal symptoms more commonly than do inhalants.

It is evident from what has been said that, though the problem is

complicated, there is no cause to belittle the importance of sensitivity in the development of asthma and allied states. The value of skin tests as a clinical procedure must necessarily be diminished by findings such as those here described. Clearly no special importance can be attached to the presence of skin sensitivity in individual cases unless there is additional evidence on other grounds. Skin testing by the intradermal method should therefore be regarded as a useful source of subsidiary information, when the patient suspects that his symptoms are induced by exposure to definite substances, or when seasonal or occupational factors are suggested by the history. The development of very large reactions usually, but not necessarily, indicates that the substance in question is of practical importance in the precipitation of symptoms. The frequent presence of skin sensitivity in apparently normal subjects implies that sensitization to a number of substances often occurs, particularly in children and young adults, and may remain latent unless revealed by artificial means.

Conclusions

1. By means of the intradermal test skin sensitivity to common inhalant substances can be shown to occur with considerable frequency among 'control' subjects.

2. The percentage of positive reactions and the proportion of large reactions are considerably greater among a corresponding group of asthmatic subjects.

3. A group of individuals, who gave a history of having experienced some atopic condition in the past, or in whose family such a condition was reported to be present, showed a greater proportion of skin reactions than a group who gave no such history, and was intermediate between these and the asthmatic group.

4. Sensitivity to inhalant substances was found to be greatest in subjects between fifteen and thirty years of age. This was found to be true for asthmatic and control groups.

5. Sensitivity to more than one extract occurred frequently in all groups, and it was exceptional to find subjects highly sensitive to one substance, who failed to react to some degree with extracts of other substances.

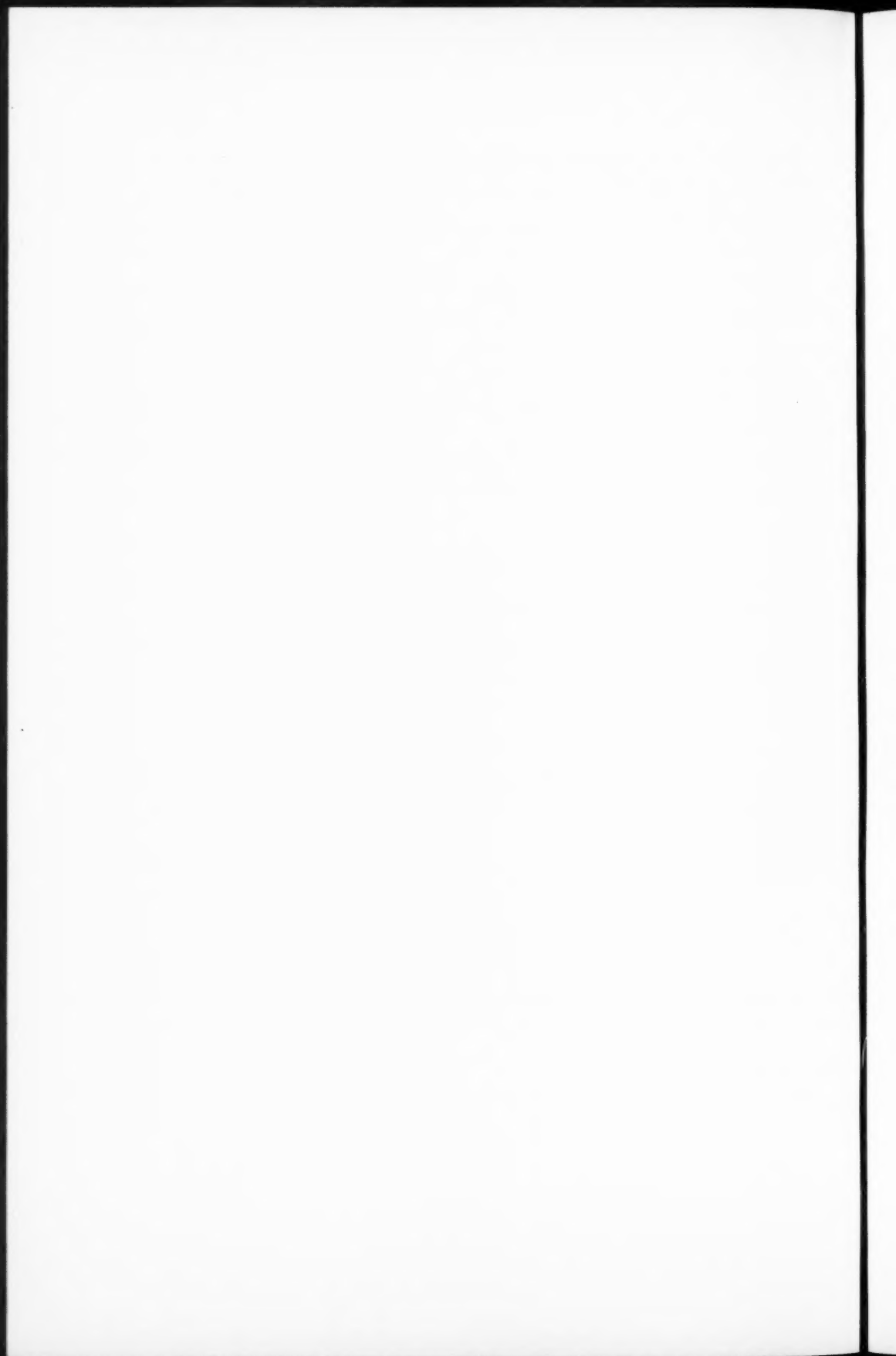
The work has been done for the Asthma Research Council with the aid of a grant from the Sir Halley Stewart Trust.

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SYSTEMATIZED ATYPICAL AMYLOIDOSIS WITH
MACROGLOSSIA¹BY F. PARKES WEBER, STANFORD CADE, A. W. STOTT,
AND R. J. V. PULVERTAFT

With Plate 5

APART from typical cases of amyloidosis, due to prolonged suppuration, tuberculous caries, and other less recognized causes, such as syphilis and Hodgkin's disease, in which the amyloidosis has notable predilection for the liver, spleen, kidneys, and intestinal mucosa, cases of so-called 'atypical amyloidosis' have from time to time been described, in which none of the recognized causes are present and in which the liver and other favourite sites of the disease are not or are only relatively little affected. Moreover, in at least some of these atypical cases the staining reactions have likewise been atypical, the characteristic metachromatic staining being faint, or obtained with relative difficulty, and not by all the recognized methods. This gives rise to the suspicion that the abnormal material present in the 'atypical' cases is not wholly amyloid, but consists, at least in part, of some chemically allied substance or substances, though true amyloid may likewise be present.

Some of these atypical cases are characterized by the occurrence of local so-called 'amyloid tumours' in the tongue, nose, and upper respiratory passages (6, 16, 27, 31, 40, 49, 51) or lungs (28) or conjunctivae (5, 38). Sometimes there are 'amyloid tumours' or circumscribed or diffuse amyloid changes confined to the skin (10, 14, 15, 19, 32, 39, 43, 48); sometimes the heart is specially selected (3, 4, 20), and sometimes the seminal vesicles or urinary bladder (8, 26, 50), though these latter are more often affected as a part of generalized amyloidosis.

In other cases the so-called amyloidosis may be more or less generalized, though not with predominance in the spleen, kidneys, liver, and other parts chiefly affected in typical amyloidosis from the recognized causes. Thus, in Steinhaus's case there was amyloidosis combined with a hyalin-like infiltration, without obvious cause, involving the heart, stomach, and intestine. The patient, a man aged 40 years, became gradually weaker, and within six months died after copious intestinal haemorrhage. There was no macroglossia. In Gerber's case, a man aged 44 years, there was diffuse amyloidosis of the bone-marrow, associated with generalized amyloidosis, but without any of the recognized causes. Compare also (2, 17, 18).

In certain cases of systematized atypical amyloidosis one of the most striking clinical features has been a diffuse, more or less symmetrical, enlargement of the tongue, 'amyloid macroglossia'. It is with such cases

¹ Received January 11, 1937.

that we are specially concerned in the present paper. In fact, as Pick (34) suggested, there seems to be a 'systematized type of atypical amyloidosis', characterized by amyloid macroglossia, sometimes combined with pseudomyotonic stiffness of involved skeletal muscles and pseudo-sclerodermic hardness of involved areas of skin. This group of cases may well be associated with Lubarsch (24), who was the first to attract the general attention of pathologists, and with Pick, who realized the symptom complex. Cases, apparently of the same kind, but in which the tongue is not obviously enlarged, may be regarded as 'incomplete' examples of this syndrome.

We shall first describe our own case and then give short extracts of more or less similar cases from the literature, all of them with enlargement of the tongue.

Present Case

1. Mrs. Daisy M., aged 48, of English birth, was admitted to Westminster Hospital on July 22, 1936, under the care of Mr. Stanford Cade, complaining of enlargement of the tongue. She was readmitted on September 17 for further investigation, and the following history was obtained.

She had not suffered from any serious illnesses except that resulting from a bad miscarriage about seven years earlier. Varicose veins in the legs were injected twelve years before. In 1933 menstruation ceased abruptly.

Her father died at the age of 73 from cirrhosis of the liver. Her mother died at the age of 63 from an unknown cause. There was no family history of vascular disorders.

About two years ago the patient began to notice that she was easily tired on walking, and this symptom was slowly progressive; it appeared to affect the whole body, not only the legs, and the latter were not then painful. She was otherwise well until August 1935, when she had a sore throat for a few days.

In October 1935 she noticed pain in the tips of all her fingers and about the shoulder joints. This was more or less constant, but became worse if she used her hands, as in knitting. The pain was considerably relieved if she crossed her arms and rested the fingers on her shoulders. About this time she noticed that the pads of her fingers were harder and pinky-red in colour.

In November 1935 some swelling of the neck under the chin was noticed, and it was at this time that the swelling of the tongue was first discovered. For about one year previously the patient had experienced difficulty in talking, which she had attributed to her dentures, but she later realized the difficulty might have been due to the swelling of her tongue. Since that time there had been no obvious alteration in the size of the tongue; her saliva had been normal in amount and character, the tongue had never been sore, and there had been no difficulty in swallowing. Apart from the slight difficulty in speech, her tongue had caused no trouble, and her chief symptom at this time was a feeling of constant tiredness.

In March 1936 she noticed pain, described as a very tight feeling, in the middle of both calves when she walked, especially uphill, so that she began to walk backwards when going uphill. Since that time there had always been pain in the calves on walking up an incline about a hundred yards; in

fact, there was a kind of intermittent claudication. If she stopped and rested for two minutes, the pain passed off and she could resume walking, but on walking the pain recurred. On level ground she had no pain if she walked slowly; she had used a walking-stick since March 1936. Her legs, from the knees to the feet, often felt cold, especially in the night.

A varicose vein in the left leg was injected in April 1936 without success; the injection was repeated a month later and the vein thrombosed. There had been no attacks of phlebitis.

On examination, after admission to the hospital, her general condition was good, and she had a good colour. The tongue was considerably enlarged, but not sufficiently to cause permanent protrusion between the teeth and prevent complete closure of the mouth. There was no ulceration or pain or tenderness. The posterior and main mass of the tongue felt hard, but not the edges, which were grooved by the teeth. Her speech was somewhat thick from the enlargement of the tongue. The heart size and sounds were normal, her brachial blood-pressure was 145/90 mm. Hg, the radial and brachial arteries did not feel thickened, the lungs were clear, and nothing abnormal was found in the abdomen. The pulsation in the superficial femoral arteries, and in the posterior tibial arteries, was good and equal on the two sides. No pulsation was felt in the dorsalis pedis arteries. The pads of all the digits were pinky-red and felt tense; they were somewhat tender on firm pressure. The nails showed no abnormality.

Her appetite and digestion had remained good, but she had lost weight. In November 1935 she weighed 9 st. 12 lb., in May 1936 10 st., in July 9 st. 5 lb., and in August 8 st. 7 lb.

Various examinations included the following:

1. *Renal function.*

(a) *Urine*: acid, contained a faint trace of albumin on one occasion; the scanty centrifuge-deposit showed a few leucocytes, epithelial cells, and red-blood cells but no casts. The specific gravity varied between 1010 and 1020.

(b) *Blood urea*: 25.9 mg. per cent. (c) *Urea clearance test*: showed an average of 86 per cent. of normal renal function.

2. *Radiographic examination.*

(a) Of chest: no abnormality except marked calcification of costal cartilages. (b) Of legs: no calcification seen in any vessel. (c) Of tongue: no abnormal shadow seen.

3. *Examination of blood.*

Haemoglobin	76 per cent.
Red-blood corpuscles	4,000,000 per c.mm.
Colour-index	0.9
White-blood corpuscles	4,800 per c.mm.
Polymorphs.	66 per cent.
Lymphocytes	30 " "
Eosinophils	1 " "
Monocytes	3 " "

Average diameter of red cells = 7.25 microns.

4. Wassermann reaction and Kahn test, negative in the blood-serum.

5. Electrocardiogram showed no abnormality. The T-waves were of small amplitude in all leads.

6. Mr. A. F. MacCallan reported that there was no evidence of any significant degree of pathological change in the retinal vessels. (He repeated his examination some days later under mydriasis and confirmed his opinion.

After a plastic operation on the tongue, with resection of a portion, had healed (Plate 5, Fig. 5), the patient left the hospital on November 26, 1936, with very little alteration in her condition otherwise.

Report of the pathologist (Dr. Pulvertaft). The first material received was a small portion of the tongue, comprising the epithelium and superficial sub-epithelial tissues, but only a few fibres of the intrinsic musculature. The tissue measured about 1 inch by $\frac{1}{4}$ inch. It was fixed in formol saline, embedded in wax, and stained by haematoxylin and eosin. The epithelium showed a moderate degree of chronic superficial glossitis. In the sub-epithelial connective tissue were a number of large circular 'whorls', most of them with a central lumen, obviously that of a blood-vessel. The presence of an elastic lamina indicated that in many, if not all, these 'whorls' the vessel was an artery. The smallest of these 'whorls' were minute, of the order of arterioles, the larger ones were easily visible to the naked eye, about $\frac{1}{4}$ inch in diameter. There was in many cases no intimal proliferation; the musculature in direct relation to the lumen was perhaps a little proliferated; the nuclei here were still prominent, but the cells had lost their outline, and appeared swollen. On approaching the periphery, however, the 'whorl' was seen to be composed of a more or less homogeneous and hyaline material, relatively free from nuclei.

These 'whorls', as has been said, were of varying size; in the case of the smaller ones, the whole process appeared to be confined to the wall of the vessel. In the case of the larger 'whorls' this was by no means certainly the case; and although the tissue in these large 'whorls' was mainly homogeneous, many minute vessels were seen in it. The appearances thus suggested that the hyaline material was deposited in voluntary muscle, concentrically from the vessel as a focus.

The voluntary muscle remote from the affected vessels appeared normal. There was no inflammatory process in the musculature.

Sections were stained in iodine and Congo-red, and showed no metachromatic staining. With Mallory's connective tissue stain, the 'whorls' stained blue; the musculature, normal in appearance, gave its usual red reaction. Stained with methyl violet, differentiated with acetic acid, no definite metachromatic staining was found. When, however, after methyl violet staining 5 per cent. oxalic acid was used, there was marked metachromatic staining, the hyaline material of the 'whorls' becoming an intense red. (See Plate 5, Fig. 1.)

The next portion of tongue examined was a wedge of muscle removed for plastic reasons. Macroscopically some of it appeared normal, but a large area was homogeneous in texture and pale in colour, cutting like cheese. Sections were prepared as before. The appearances were very striking. The superficial 'whorls' previously noted were again present, but it was possible to ascertain that the changes in the vessels were nodular, and the hyaline material often appeared as an eccentric bulge on the vessel. The intrinsic musculature of the tongue was converted into an almost homo-

geneous mass of hyaline material, in which only small areas of recognizable voluntary muscle persisted. Metachromatic staining was not found either with paraffin or frozen sections when iodine, Congo-red, and methyl-violet-acetic acid were used. Paraffin sections tended to give better results than frozen sections. With Mallory's stain the surviving muscle was red, the abnormal blue. With methyl-violet-oxalic acid staining there was some metachromatic reaction; it was poorly marked. Frozen sections were stained with Sudan III, and examined under polarized light. The results were negative. (See Plate 5, Fig. 2.)

These examinations confirmed the earlier one, and indicated that the process involved the intrinsic muscles of the tongue as well as the musculature of vessels.

A portion of gastrocnemius muscle was next forwarded. In this case the material was very difficult to cut. It was embedded and stained as before. There was no evidence of change in the voluntary muscle. The vessels, however, large and small, showed the same medial changes, again markedly nodular and eccentric in distribution. There was no doubt in this case that the greatly increased transverse diameter of the vessel was due to a change in the medial coat. (See Plate 5, Fig. 3.)

The final material received was a small piece of tissue from the pad of a finger-tip. In this case fixation in Schaudin's solution was employed. There was nothing abnormal in the superficial epithelium, sweat glands, nerves, or connective tissue. Large vessels were present in the deepest part of the tissue, and these all showed gross changes in the medial coat, of the type already described; the intima was normal. In this case the nodular distortion by this hyaline material was unusually pronounced. No recognizable voluntary muscle was present, but the appearances suggested a similar change to that seen in the tongue muscles, in this case in certain connective tissue or perhaps degenerate muscle fibres. Methyl-violet staining followed by 5 per cent. oxalic acid gave excellent metachromatic staining. It was noted that after twenty-four hours the hyaline nodular areas became almost black in contrast with normal tissue. No other stain gave metachromatic staining, though as usual Mallory's stain gave a blue reaction in the abnormal tissue. (See Plate 5, Fig. 4.)

Tests on the patient included a measurement of the disappearance of intravenous Congo-red. Twenty-nine per cent. was found to disappear in one hour, which is within normal limits, though high.

The histological study of the material suggested that there was a widespread abnormality in the medial coat of arteries, both large and small, and that in the case of the tongue, and possibly of the fingers, this change was also present in voluntary muscle.

Initially nodular and focal, the change eventually becomes diffuse, enlarging the vessels enormously. Apparently the change first shows as a swelling of involuntary muscle fibres, as from imbibition.

The histological change appears to be of similar nature to that found in

amyloidosis. Amyloid is merely a name given to a hyaline structureless material in vessels and tissues which is metachromatic by recognized stains, of which only one, methyl violet and oxalic acid, gave good results in this case. Any lipid or cholesterol-like material is excluded in these changes.

Whether the change is one in the metabolism of the cell, or the result of absorption of a circulating abnormal substance, is conjectural. The results of the intravenous Congo-red test suggest that the change was localized, and that any circulating abnormal constituent was small in amount.

Abstracts of more or less Similar Cases from the Literature, all of them with Enlargement of the Tongue

2. Königstein's cases (1925). A man, aged 60 years, died with macroglossia, which was however not a presenting symptom, difficulty in swallowing, weakness in arms and gradual cachexia. His illness apparently commenced two years before his death, after an attack of facial erysipelas. A widely distributed nodular or papular dermatosis had been a chief manifestation from the commencement, and a biopsy examination of the skin had enabled the diagnosis of amyloidosis to be made during life.

The necropsy, with microscopical examination, showed that the amyloidosis involved the whole digestive tract from the tongue to the anus, the heart, veins, the mucosa of the urinary bladder and urethra, the skeletal musculature, the fatty tissue generally, and the skin.

Königstein's second case (1925) was that of a woman, aged 60 years, with chronic nephritis, ascites, bilateral hydrothorax; amyloidosis of heart, spleen, lungs, fatty tissue, as well as a nodular amyloid change in the skin. There was also a certain amount of amyloidosis of the tongue and nasal mucosa, but no definite macroglossia as in Königstein's first case.

3. Lubarsch's first case (1929). A man, aged 54 years at the time of his death in March 1926. At the age of 46 years (1918), after a shock in the War, he suffered from paralysis in various groups of muscles, and remained permanently under hospital treatment. Digestive disturbances developed, and in the last year there was muscular stiffness; finally the tongue became hard and thickened, especially the right half, and there was trouble in swallowing. In the clinical diagnosis myotonia, sclerodermia, and lingual cancer were spoken of. The necropsy, with microscopical examination, showed that the 'growth' in the tongue was of amyloid nature, and that there was a generalized amyloidosis of extraordinary degree and localization—involving the skin, digestive canal, serous membranes, lungs, heart, and skeletal musculature. The amyloidosis in this extraordinary case relatively spared the parts generally chiefly involved, namely, the spleen, kidneys, adrenals, liver, intestinal mucosa, salivary glands. The nodular character of the amyloidosis was likewise remarkable, and no recognized cause for the disease could be ascertained.

Lubarsch at the same time described two other, in many respects similar, cases of atypical amyloidosis, in which the striped and unstriped muscles were involved, but in which there was no suggestion of definite amyloid macroglossia.

4. Warren's case (1930). A woman, aged 54 years, with a sore, swollen tongue. The necropsy showed amyloidosis of tongue, heart, stomach,

oesophagus, intestines, diaphragm, urinary bladder, gall-bladder, striped muscles (rectus abdominis), subcutaneous tissue of cheek, and mesenteric blood-vessels. In the uterus it was a leiomyoma which especially showed the change. The parenchymatous viscera, liver, spleen, and kidneys, were not involved, though there was a hyaline change in their blood-vessels.

5. Gerstel's case (1932). A married woman, aged 52 years at the time of her death in May, 1930. There was nothing special in the family or previous history. In May, 1928, swelling of jaw and tongue and of the lymphatic glands below the lower jaw appeared. These swellings persisted till patient's death. On account of the macroglossia the teeth could not be closed; a diffuse sarcomatous infiltration of the tongue was thought of. About May, 1928, swelling and hardening of the skin of the neck commenced, and slowly increased during the following two years till the patient's death. The patient's general condition gradually became worse. During the last months the macroglossia increased with dyspnoea, oedema of the feet, asthenia, diarrhoea, sometimes blood in the faeces, but no vomiting. The final clinical diagnosis was cancer of the floor of the mouth.

At the post-mortem examination Professor L. Pick recognized the case at once as one of so-called 'atypical amyloidosis', with diffuse symmetrical amyloid macroglossia, amyloidosis of the skin, connective tissue and musculature of the neck, of the upper and middle portions of the oesophagus, of the stomach, intestines, and mesentery. Pseudo-membranous colitis and proctitis were present. The pancreas, liver, spleen, kidneys, lymph-glands and adrenals were not affected, apart from an amyloidosis of some of the blood-vessels. In the heart the myocardium and cardiac valves were free, but there was amyloidosis of the subepicardial fat. There was amyloidosis of the connective tissue and blood-vessels of the diaphragm, but not of the diaphragmatic musculature itself.

6. Gottron's case (1932). A married woman, aged 46 years, with good family history. For the last three years there was difficulty in muscular movement; for two years increasing hoarseness and thickening and hardening of skin of face and neck (scleroderma amyloidosum); for some months enlargement of the tongue. In the hospital it was noticed that other parts of the skin were affected. Biopsy examination showed the presence of amyloidosis of skin and muscles. Gottron's case was the first in which this kind of generalized atypical amyloidosis could be diagnosed with certainty during life. X-ray examination of the stomach and intestines suggested that the unstriped musculature of the digestive tract was probably also involved.

7. Mollow and Lebell's case (1932). A man, farm labourer, aged 60, after suffering from a varicose ulcer, complained of abdominal pains and constipation, and later of enlargement of tongue and difficulty in swallowing and speaking. There was trouble in walking, and meteorism and spastic constipation. The skeletal muscles, especially of the back and lower limbs, were of athletic appearance and hypertonic; there was no myotonic reaction. Superficial ulceration of the enlarged tongue developed, and small white cutaneous nodules of amyloid. Death was due to cardiac weakness. The necropsy showed systematized amyloidosis with atypical staining reactions affecting the tongue, diaphragm, skin, heart, suprarenals, choroid plexus in the brain and pia mater. There was little amyloidosis of spleen and liver.

8. Balyeat's case (1935). A man, aged 60 years at the time of his death, in January 1935. He had an enlarged tongue with difficulty in

swallowing and talking, which had first troubled him about September 1934. About the same time the submaxillary lymph-glands became enlarged. Small erosions on the tongue used to come and disappear spontaneously. The tongue became more swollen and the patient felt weaker. Ordinary physical examination was negative, except for secondary anaemia, arteriosclerosis and myocardial degeneration. On January 3 he dropped dead. The necropsy showed that the macroglossia was due to amyloidosis, with amyloid deposits throughout the tongue muscles. According to the account given no other structures showed amyloid deposits.

9. Michelson and Lynch's case (1934). A man, aged 54 years, with progressive macroglossia and a striking change in the skin and in the mucous membrane of the mouth and anus, and with increasing general weakness. There was no post-mortem examination, but biopsy examination during life showed that the macroglossia and the changes noted in the skin and mucous membranes were due to amyloidosis. It should be noted that the fingers became tensely swollen and tender, and small localized purpuric spots appeared following the slightest trauma. A very remarkable clinical feature of the case was constant Bence-Jones proteinuria. The association of Bence-Jones proteinuria in cases of undoubted myelomatosis with atypical amyloidosis is discussed later.

10. Perla and Gross's case (1935). A woman, aged 53 years, was admitted to hospital for signs of cardiac failure, cyanosis, and ascites. There was also great anaemia. The clinical diagnoses were congestive heart failure and a malignant tumour of the tongue. She died with a sudden attack of dyspnoea and circulatory collapse two weeks after admission. The post-mortem examination showed amyloidosis involving chiefly the tongue, heart, kidneys, lungs, and gastro-intestinal tract; the diaphragm and skeletal muscles were likewise to some extent involved. In this case none of the recognized causes of typical amyloidosis were present.

The authors likewise described two other cases of atypical amyloidosis, without recognized aetiological factors, but in neither of them was the tongue specially involved.

11. Reimann, Koucky, and Eklund's case (1935). A woman aged 43 years at the time of her death in January 1935. The illness had lasted two years. About three years before the patient's death her tongue had been noted to be thick and red and it felt to her as if blistered. The tongue continued to enlarge and the skin over the chin became hard. The condition was regarded as malignant, but afterwards a clinical diagnosis of amyloid disease of the tongue, skin, and (probably) of the genitalia and mediastinum was made, and confirmed by biopsy histological examination of the tongue, skin, and vaginal wall. This was finally confirmed by the post-mortem examination. The 'whorl-like' appearances of the amyloid arteries seen in transverse section in the tongue was very similar to the appearances found in our case and in Gerstel's case.

The association of amyloidosis with myelomatosis has been stressed by Magnus-Levy (25). In the many examples of this association referred to by him the amyloidosis seems to have been generally 'atypical', that is to say, the deposits were mostly nodular, and the amyloidosis when systematized, did not specially involve the abdominal viscera usually selected in typical amyloidosis. In a case of myelomatosis with Bence-Jones proteinuria, described by Parkes Weber (46) in 1903, at the necropsy the tongue was

ulcerated and hardened, and in microscopical sections, stained with methyl violet, a good deal of amyloid or closely allied substance was found, though none was discovered in similarly stained sections of the liver, spleen, and kidney. The rosy coloration with methyl violet showed that the substance in question, if it was not actually amyloid, was a very closely allied substance. This was probably the first case of myelomatosis in which any kind of amyloidosis was detected. At that time the local amyloidosis was attributed to what was supposed to be a local tertiary syphilitic lesion. What this association of amyloidosis with myelomatosis means is not known. Magnus-Levy has suggested that both Bence-Jones protein and amyloid in cases of myelomatosis may be derived from the myelomatous bone-marrow. He has referred to other cases of myelomatosis in which there was amyloidosis of the tongue without any obvious macroglossia, and in one of our series of the Lubarsch-Pick syndrome (Case no. 9, Michelson and Lynch) obvious amyloid macroglossia was associated with Bence-Jones proteinuria, but no post-mortem examination was made to see if myelomatosis was present or not. The association has been recently discussed also by Rosenblum and Kirshbaum (37) and by Robertson and Brunsting (37).

Discussion and Conclusions

Apart from the classical cases of generalized amyloidosis due to the ordinary recognized causes, there is a group of cases in which some substance or substances allied to amyloid are systematically deposited in various tissues and organs of the body, notably in a nodular or tumour-like way, with preponderance in certain parts. Such cases have been classified under the general heading, 'systematized atypical amyloidosis' and in the most typical of them the tongue has been specially involved, with the formation of a diffuse more or less symmetrical macroglossia. This condition we regard as the complete 'Lubarsch-Pick syndrome'. Of the eleven patients five were men and six were women; their ages varied from 43 to 60 years. These cases must be distinguished from those of isolated so-called 'amyloid tumours' in the tongue and upper respiratory passages referred to at the commencement of this paper.

In our case the muscular coats of the small arteries are infiltrated by the substance or substances in question, which must be regarded, like typical amyloid, as abnormal metabolic products. Whether these substances are produced locally or imbibed from the circulating blood, their accumulation has given rise to a thickening of the walls of the small arteries and swelling of the striped muscle of the tongue. Most characteristic in the microscopic examination of our case are the large ring-like compartments or 'whorls' in the submucosa of the tongue, formed by great enlargement of the muscular wall of the little arteries as seen in transverse section. They are obviously analogous to or paralleled by the similar ring-like appearances in the tongue from Reimann, Koucky, and Eklund's case, as illustrated in

their paper, and in the jejunal submucosa from Gerstel's case (Fig. 11 on p. 481 of his paper). Dr. W. Freudenthal has suggested to us that the primary change may be a kind of hypertrophy-hyperplasia of the muscular coats of the small arteries, which later on proceeds to the changes characterized by the metachromatic staining of 'atypical amyloidosis'. If so, it seems to us that the stimulus giving rise to the hypertrophy-hyperplasia may be the presence of some abnormal metabolic product, which later on is deposited, so as to give rise to the appearances of 'atypical amyloidosis'. In a remarkable case of cutaneous non-diabetic xanthomatosis, described by one of us (F. P. W.), Dr. W. Freudenthal accounts for the cutaneous tumour-like nodules of large clear cells by suggesting that the lipid (cholesterol) excess has acted as a stimulus to the production of these cells before it has become deposited in the cytoplasm of the cells to form typical 'xanthoma cells' (47). We mention this by way of analogy.

In some cases apparently true amyloid is also deposited, as in typical cases of generalized amyloidosis due to the recognized causes. In regard to the question of whether the deposits in our case of 'atypical amyloidosis' can be regarded as true amyloid or not, one of us (F. P. W.) was formerly very familiar with the methyl-violet staining of true amyloid in tuberculous cases and, notably, in cases of so-called 'secondary chronic interstitial nephritis', in which latter cases minute amyloid spots in the renal glomeruli, the existence of which was not generally known, usually showed up brilliantly with methyl violet, especially when oxalic acid was employed instead of acetic acid, for decolorization. It may be confidently asserted that the metachromatic staining in our present case is not quite the same as that in the typical amyloid cases. Elaborate reviews of what is known about human amyloidosis and experimental amyloidosis in animals have been written by Eppinger, Leupold, Letterer, Waldenström, and Puccinelli, but there is still uncertainty as to the real nature of amyloid, and wax-like, and hyaline deposits of the same group. No biochemical investigations have been carried out in our case.

In our case the skin has not yet become involved, as it was in some others (cases 2, 3, 5, 6, 7, 9, 11).

The disturbance in gait resembling intermittent claudication may be accounted for by inability of the thickened arterioles to enlarge when demand is made on them for any unusual blood-supply, or else it may be due to actual involvement of the striped muscles and may thus be analogous to what Pick called pseudo-myotonic stiffness of amyloid skeletal muscles.

The redness and pain or paraesthesia of the ends of the fingers and the tense turgidity of the finger-pads may be accounted for by involvement of the arterioles, or by supposing that the 'glomus' anastomoses (Masson) have been damaged, so that they can no longer act as safety valves to short-circuit excess of blood directly from the arterioles into the venules. This sign may, however, represent an early stage of the tensely swollen and tender fingers in Michelson and Lynch's case.

Our case is apparently the first one with this type of macroglossia to be described in England, and is one of the first examples of the Lubarsch-Pick syndrome recognized during the patient's life. The intermittent claudication and the finger-end phenomena should be specially noted. Like many other rare conditions clinically the disease is startling and pathologically it is puzzling. But it is not unknown, as we were at first inclined to suppose.

We have to acknowledge kind assistance and suggestions from Dr. W. G. Barnard, Prof. G. W. de P. Nicholson, and Dr. W. Freudenthal.

Summary

Eleven cases of systematized atypical amyloidosis with macroglossia which we have termed the complete form of the 'Lubarsch-Pick syndrome', have been described and discussed—one of our own and the others from the literature. In our own case (Case 1) and three other cases (Cases 6, 9, and 11) the diagnosis has been made and confirmed by (biopsy) microscopical examination during life, but in the other cases there are necropsy accounts. In one case (Case 8), according to the published post-mortem examination, the atypical amyloidosis seems to have been limited to the enlarged tongue.

Though the exact cause is unknown, the syndrome is apparently due to a metabolic disturbance of some kind, and it is noteworthy that a kind of atypical amyloidosis may occur in association with myelomatosis (multiple myeloma). The relatively frequent association of two such rare conditions can hardly be a mere coincidence. The nature of their connexion, which at present can only dimly be guessed at, is probably of great pathological importance.

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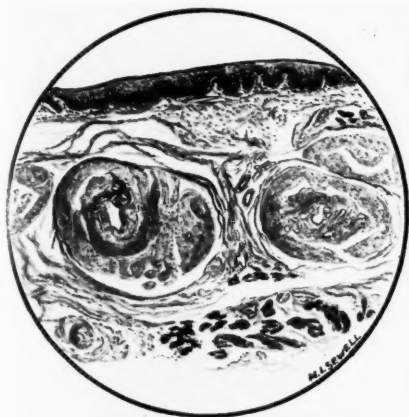


FIG. 1. From the tongue, superficial



FIG. 3. Muscle of leg

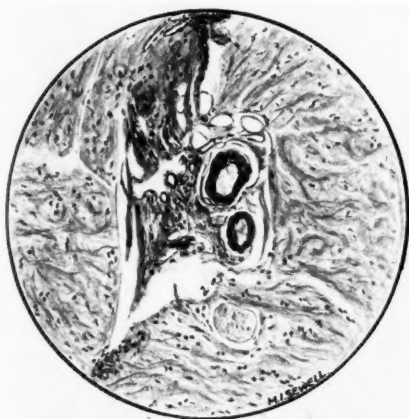


FIG. 2. From the tongue, deep



FIG. 4. From the finger pad



FIG. 5. Appearance of the tongue after resection of a portion

ACHLORHYDRIA, ANAEMIA AND SUBACUTE COMBINED DEGENERATION IN PITUITARY AND GONADAL INSUFFICIENCY¹

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With Plate 6

IN the present paper we describe a group of cases of hypopituitarism and hypogonadism apparently secondary to insufficiency of the anterior lobe of the hypophysis. Of the six patients five had achlorhydria even after the injection of histamine. One had a hypochromic anaemia, the others a hyperchromic anaemia or subacute combined degeneration. We believe that the pituitary defect was the initial lesion in these patients, and that it was followed by achlorhydria, which induced an achlorhydric dyshaemopoietic anaemia, but we have no proof that this was the actual sequence of events.

The association of pituitary disease with an Addisonian anaemia has apparently not been recorded in the literature. We shall refer later to published cases which appear to be examples of hypopituitarism complicated by subacute combined degeneration. Fanconi (1927) described a remarkable family in which three brothers developed a hyperchromic megalocytic anaemia at about six years of age and quickly succumbed. All suffered from infantilism with brownish discoloration of the skin and very small testes. The anaemia was not characteristically Addisonian in type, as there was free hydrochloric acid in the gastric secretion, no excess of bile pigments in blood or urine, and the bone-marrow was hypoplastic. There was in addition a haemorrhagic tendency, which had also been exhibited by other members of the family. The pituitary was examined in one of these boys:—The anterior lobe was well developed with very numerous eosinophil cells, but only scanty basophil cells, and an average number of chief cells. The middle lobe was poorly developed, the posterior lobe well developed with moderately cellular glia.

Fanconi (1927) also reported the case of a boy with pseudo-hypertrophic muscular dystrophy whose testes were undeveloped and who presented a hyperchromic megalocytic anaemia. Megalocytic anaemia, infantilism, and hypo-gonadism are occasionally observed in coeliac disease.

There is a classical theory that chlorosis was due to gonadal or endocrine disorder, but in view of the loss of haematinic substances in menstruation and pregnancy, we can attach no great significance to the co-existence of endocrine disease and hypochromic anaemia in the female. In the male,

¹ Received February 10, 1937.

idiopathic hypochromic anaemia is uncommon and the association of eunuchoidism and hypochromic anaemia is therefore more significant. Few cases have hitherto been recorded. Those reported by Naegeli (1917) were examples of myotonia atrophica, a curious hereditary malady in which widespread lesions such as cataract, testicular atrophy, acrocyanosis, premature baldness, and emaciation, occur in association with muscular dystrophy. Little is known of the pathology of this disease, but anaemia is by no means constant, the blood being noted as normal in several cases in which the testes had atrophied. Filo (1933) described a severe and unexplained microcytic hypochromic anaemia of a relapsing type in a lad of 16, whose testes were small and undescended and whose libido was subnormal. The gastric secretion was normal and the anaemia responded well to iron. Gardiner Hill (1931) described a case of chlorotic anaemia in a boy of 17, mentally and physically backward, whose sex development was delayed in a characteristic eunuchoid manner; there was a history of vegetarianism and the anaemia responded to iron. Burger and Witts (1934) in a paper on hypochromic anaemia in men noted that males with unexplained anaemia were often of asthenic habit and looked younger than their age. In all these examples of anaemia associated with eunuchoidism or infantilism the anaemia appears to have been of a hypochromic type, responsive to iron, and no abnormalities were noted in the gastric secretion.

Case Reports

Case 1. J. H., male, aged 52, was seen in February 1929 in the out-patient department of the Clinic for Internal Medicine of the University of Amsterdam.

History. During the previous six years he had gradually lost his hair and had become impotent. He complained of undue fatigue, so that he could not do his ordinary work, of failing memory, irritability, scaling of the skin, and crumbling of the nails. He had noticed perspiration and tremor and his weight had decreased, but he had been taking thyroid preparations for a long time. He was married, with four sons and two daughters all in good health. Two other children had died young.

Physical condition (February 1929). Height 1.71 metres; weight 67.2 kg. Almost completely bald, with absent eyelashes and eyebrows; a few scattered hairs on cheeks and lips (Plate 6, Fig. 1); pubes, chest, and axillae almost hairless. No atrophy of tongue papillae. Examination of the heart, lungs, and abdomen showed no abnormality. Systolic blood-pressure 140 mm. mercury. Testes soft, but of normal size. Prostate normal.

Investigation. Urine normal. Radiograms of skull showed a normal sella turcica. Wassermann and Sachs-Georgi reactions negative. Basal metabolic rate +3 per cent. (during thyroid treatment).

A diagnosis of polyglandular insufficiency, affecting especially the testes and anterior lobe of the pituitary was made. The patient was discharged well enough to resume a part of his normal work.

In June 1930, he was readmitted with a six months' history of increasing

lassitude, palpitation, dyspnoea, loss of appetite, and loss of weight. On examination the physical condition was unchanged: the spleen could not be felt and there was no abnormality in the nervous system. The basal metabolism was +9.6 per cent. and the blood count showed a moderate hypochromic anaemia with red cells 4,200,000 and haemoglobin 60 per cent.

After five weeks' treatment with an early preparation of the anterior lobe of the pituitary (the efficacy of which must now be considered uncertain), the patient's condition had deteriorated and a severe hyperchromic anaemia was discovered. The red cell count was then 1,290,000 per c.mm., and the haemoglobin 30 per cent., leucocytes 2,900 per c.mm., with a relative lymphocytosis: the stained film showed normoblasts and macroblasts, megalocytosis, and anisocytosis, punctate basophilia, slight polychromasia and poikilocytosis, platelets 65,000 per c.mm. The indirect van den Bergh reaction was 3.4 units, and an excess of urobilin was found in the urine. A fractional test meal with histamine showed complete achylia: radiograms of the stomach and bones showed no abnormality. The patient therefore had developed while under observation a typical pernicious anaemia.

He was treated with dried stomach powder and there was a reticulocyte response of 12 per cent. on the sixth day. At the end of five weeks the red cell count was nearly 5,000,000 per c.mm., the haemoglobin 77 per cent., and the patient's condition had improved so much that he was able to return to his work.

He continued to take this treatment and felt well until July 1933, when he began to complain again of undue fatigue, dizziness, dyspnoea, palpitation, and in addition of unsteadiness in walking, tingling and numbness in the legs and feet, and a sense of constriction around the upper abdomen. He began to have attacks of soreness of the tongue. In view of the deterioration in his condition a potent liver extract was substituted for the stomach preparation which he had been taking.

He was readmitted to hospital in October 1933, still with complete alopecia, soft but otherwise normal testes, and a normal prostate. He was found, however, to have developed signs of subacute combined degeneration of the spinal cord, loss of sense of position in the toes and sense of vibration in the legs, loss of discrimination of figures written on the skin, unequal knee-jerks, and absence of the left ankle-jerk. The plantar reflexes were flexor. The red cell count at this time was 3,750,000 per c.mm., and the haemoglobin 90 per cent., the mean corpuscular diameter 8μ and the mean corpuscular volume 125 cu. μ .

Discontinuance of liver therapy for two weeks caused a relapse in the blood picture, and a resumption of intramuscular therapy a further typical response, with a reticulocytosis of 11.5 per cent. on the eighth day. The basal metabolic rate at this time was -2.9 per cent. New radiograms of the skull showed a normal sella turcica, the visual fields were normal and there was a normal sugar tolerance curve. The patient was discharged at the end of 1933, with a diagnosis of two distinct conditions, pernicious anaemia with subacute combined degeneration of the cord, and an endocrinopathy probably attributable to dysfunction of the anterior lobe of the pituitary.

His condition remained satisfactory on treatment with a stomach preparation by mouth until October 1935, when he was readmitted suffering from angina pectoris. In the electrocardiogram there was an inverted T-wave in lead i, R. T. deviation and an inverted T-wave in lead ii, and R. T. deviation in lead iii. There were no signs of heart failure. The blood count at

this time showed 4,090,000 red cells per c.mm., 94 per cent. haemoglobin, 8,400 white cells, and 150,000 platelets per c.mm. The alopecia remained unchanged.

In May 1936, the anginal attacks had ceased and a considerable improvement in the neurological condition had occurred. There was little ataxia of the legs: appreciation of figure writing on the skin, perception of pin prick and touch, and sense of position in the lower limbs were normal. The knee- and ankle-jerks were present and equal, the latter being sluggish.

Summary. The case is described of a man of 52 years of age with symptoms and signs attributable to a deficiency of the anterior lobe of the pituitary, who developed complete gastric achylia, a megalocytic hyperchromic anaemia which reacted in a typical manner to liver therapy, and a combined degeneration of the spinal cord.

Case 2. B. H., female, aged 35, was admitted in 1928 to the Clinic for Internal Medicine of the University of Amsterdam.

History. Menstruation with normal and regular periods began at the age of 15 years. Normal confinements occurred at the ages of 24 and 26, both children being breast-fed. The patient's third confinement occurred when she was 28 years of age, and was complicated by severe bleeding, the patient being so weakened by this bleeding that she could not feed the child. She never menstruated again. Always pallid, she became very pale, sensitive to cold, and suffered for some years from headaches. Her hair started falling out rapidly and she lost her eyebrows (presumably after burning them).

Physical condition (1928). Pale and ill, height 1.62 metres, weight 1.55 kg., scalp hair scanty, complete absence of pubic and axillary hair. Blood-pressure 95/65 mm. mercury. No abnormality in the nervous system.

Investigation. Red cells 3,610,000 per c.mm., haemoglobin 50 per cent., colour index 0.7, leucocytes 6,400 per c.mm. Differential count: polymorphonuclears 61 per cent., lymphocytes 27.5 per cent., monocytes 3 per cent., eosinophils 6.5 per cent., and basophils 2 per cent. A fractional test meal showed a small amount of free acid present in one specimen of gastric juice only and a low total acidity. Urine: no albuminuria; some casts constantly present. Renal efficiency tests suggested a slight impairment of the renal function. Discharged from hospital improved after some weeks.

In March 1934 she had an attack of cystitis with incontinence and dysuria, from which she recovered after treatment for three weeks with diet and rest. Two months later the patient was readmitted to hospital with a submandibular abscess. After incision of the abscess, the removal of several bad teeth was accompanied by a severe haemorrhage which was controlled with difficulty. The patient was severely ill and was given two transfusions of blood.

Physical condition (March 1934). Hair of scalp thin, with scanty eyebrows and absent pubic and axillary hair; eyelashes present. Face expressionless with sunken eyes and features (Plate 6, Fig. 2). Voice somewhat hoarse. No oedema. Heart, lungs, nervous system, and visual fields normal. Blood-pressure 110/50 mm. mercury.

Investigation. Stereoscopic radiograms of skull showed no abnormality of sella. Basal metabolic rate -30 to -37 per cent. Fractional test meal showed a low total acidity, and the presence of a trace of free hydrochloric acid in one specimen only, taken fifteen minutes after the injection of histamine. Blood counts before and after transfusion showed an anaemia which

had become hyperchromic in type; red cells one month after transfusion 3,430,000 per c.mm., and haemoglobin 75 per cent. Urobilin reaction in the urine strongly positive.

A diagnosis of hypofunction of the anterior lobe of the pituitary was based on the finding of complete amenorrhoea, extensive loss of hair with sleepiness, a dry skin, shrunken face (Plate 6, Fig. 2) and a decreased basic metabolic rate, all coming on after a confinement at the age of 28 years. Against a diagnosis of myxoedema was the absence of any swelling of the subcutaneous tissues and of any sign of the 'full moon' face that is found in patients with myxoedema. Further, complete amenorrhoea and complete loss of pubic and axillary hair is rare in myxoedema. An attempt to confirm the diagnosis by treatment with a preparation of thyrotropic hormone from the anterior lobe of the pituitary was abandoned on account of severe reactions after each injection. Treatment with iron and thyroid by mouth led to an improvement, but not to the spectacular change in condition which is seen in cases of myxoedema.

She was seen again in July 1934, when she was pale but had no definite complaints. Her blood count at this time was red cells 3,230,000 per c.mm., haemoglobin 82 per cent., colour index 1.27, leucocytes 8,900 per c.mm. Differential count: polymorphonuclears 58 per cent., lymphocytes 35 per cent., eosinophils 4 per cent., monocytes 3 per cent. A stained film showed slight anisocytosis, but neither primitive cells, poikilocytosis, polychromasia, nor punctate basophilia. Mean corpuscular diameter 8.156μ (Price-Jones method). Mean corpuscular volume 100 cu. μ . Urobilin and urobilinogen reactions in the urine just positive.

Summary. The case is described of a woman of 43 years of age with symptoms and signs attributable to an insufficiency of the anterior lobe of the pituitary, who developed almost complete gastric achylia and a megalocytic hyperchromic anaemia.

Case 3. v. L. v. d. Sl., female, aged 53, was admitted in 1930 to the Clinic for Internal Medicine of the University of Amsterdam.

History. At the age of 43 she began to complain of headache and failing vision. Within a year she was blind. She was at times dizzy but had neither nausea nor vomiting. She had had eight children, and the menopause had occurred at the age of 38 following an abortion.

Physical condition (1930). Weight 57 kg. Complete absence of pubic and axillary hair. Mitral stenosis and regurgitation, no evidence of heart failure. Nervous system: bilateral primary optic atrophy, no reaction of pupils to light and little on convergence, nystagmus on looking to the right. Sluggish knee-jerks and absent ankle-jerks. Plantar reflexes flexor.

Investigation. Radiograms of the skull showed enlargement of the sella turcica with erosion of the anterior clinoid process and disappearance of the dorsum sellae. The floor of the sella was irregular. Wassermann and Sachs-Georgi reactions negative in the blood and cerebrospinal fluid. On lumbar puncture the cerebrospinal fluid pressure was 100 mm. of mercury, and there was no sign of a block. Nonne reaction positive; 2.7 cells per c.mm. Urine and blood normal. Red-blood corpuscles 5,440,000 per c.mm., haemoglobin 89 per cent., leucocytes 6,700. Differential count: polymorphonuclears 73 per cent., eosinophils 1 per cent., lymphocytes 18 per cent., and monocytes 8 per cent.

A diagnosis of intrasellar tumour was made, and this was thought, on

clinical grounds, to be a benign chromophobe adenoma of the anterior lobe of the pituitary.

Three years later (1933) the patient was readmitted to hospital with symptoms attributable to her cardiac condition. She complained of feeling tired and often dizzy, of cold hands and feet, of headache, and of vomiting and heartburn.

It was found on examination that her cardiac condition was little changed.

Her pulse was regular and of small volume, her liver was just felt, her spleen not palpable, and there were no signs of heart failure. The primary optic atrophy, fixed pupils and nystagmus on looking to the right, found at the time of her previous admission were still present, but she had developed in addition hypotonia in the lower limbs with an ataxic gait, sluggishness of the knee-jerks and absence of the ankle-jerks, loss of vibration sense and discrimination of figures written on the skin, and bilateral extensor plantar responses.

On lumbar puncture the pressure of cerebrospinal fluid was 210 mm. Pandy reaction positive. Wassermann, Sachs-Georgi, and Nonne reactions negative. The blood count at this time was: red cells 3,780,000 per c.mm., haemoglobin 86 per cent., leucocytes 3,800 per c.mm. Differential count: polymorphonuclears 55 per cent., eosinophils 3 per cent., lymphocytes 32 per cent., and monocytes 10 per cent. Platelets 250,000 per c.mm. Mean corpuscular diameter 7.2 μ . Mean corpuscular volume 58 cu. μ . A fractional test meal with histamine showed complete gastric achylia.

The patient, therefore, had developed the neurological picture of subacute combined degeneration of the cord with complete gastric achylia.

Summary. The case is described of a woman of 55 years of age, suffering from a slowly growing intrasellar tumour and presenting symptoms of an insufficiency of the anterior lobe of the pituitary, who developed, twelve years after her blindness was complete, a complete gastric achylia and the neurological picture of subacute combined degeneration of the cord.

Case 4. Si., male, aged 58, was admitted in June 1936 to the Clinic for Internal Medicine of the University of Amsterdam.

History. Six years previously the patient had begun to complain of pain in the back and of excessive fatigue. In January 1935 he was carefully examined by a neurologist, who found that he had a blood-pressure of 170/100 mm. of mercury, but no abnormal signs in his nervous system. In September 1935 he had to give up his work and was seen again by the same neurologist, who found that his blood-pressure had increased to 195/100 mm. of mercury, and that his ankle-jerks were absent. In October 1935 he was examined in a medical clinic and found to have a blood-pressure varying between 235/100 and 180/85 mm. of mercury, and absence of ankle-jerks. His blood count at this time was: red cells 4,770,000 per c.mm., haemoglobin 81 per cent., colour index 0.85, leucocytes 5,900 per c.mm. Differential count: polymorphonuclears 57 per cent., lymphocytes 29 per cent., eosinophils 4 per cent., basophils 2 per cent., monocytes 8 per cent. Renal efficiency tests showed no abnormality; urea clearance 97 per cent.

At the time of his admission to hospital in June 1936 he complained of a definite aversion from food, which made him vomit. Apart from this he had no dyspeptic symptoms. He was tired by the least exertion, and quite unable to work. He often felt dizzy and had a beating and thumping sensation in his head. He felt the cold unduly, was constipated, and had pains

in the shoulders and elbows. He complained of tingling in the feet, especially when standing or walking.

Physical condition (June 1936). Height 1.70 metres, weight 63.7 kg. A man of sickly appearance and expressionless face. Speech slow but mentality normal. Skin dry and thin, especially over the extremities, where the muscles were atrophic and the skin like cigarette paper. Hair of head a little thin, and of eyebrows normal. Eyelashes scanty. Pubic and axillary hair absent. Scanty beard (shaves twice a week). No abnormality of the heart, lungs, and abdomen; liver and spleen not felt. Systolic blood-pressure from 145 to 185 mm. of mercury and diastolic from 95 to 100 mm. The spine showed a dorsal kyphosis, with slight stiffness but no pain on palpation or movement. Movement of elbow joints and joints of feet normal. Considerable limitation of movements of shoulders and hips. Nervous system: fundi normal except for slight pallor of the left disc. Visual fields: on the left side a defect in the temporal field for red and a less extensive one for blue; on the right side a slight defect in the temporal field for red only. Knee-jerks present, left brisker than right. Ankle-jerks absent. Plantar responses: right extensor, left flexor. Appreciation of pain, touch, and figure writing on the skin normal. No ataxia.

Investigation. Radiograms of the shoulder joints showed a humerus with thin corticalis, and decalcification was evident in the bones near the elbow, and in the hands and feet. Radiograms of the spine showed a few hook-like exostoses. The pelvis appeared normal. Radiograms of the skull showed some decalcification and slight enlargement of the sella turcica, with possibly some destruction of its posterior wall. A fractional test meal with histamine showed complete gastric achylia. The Wassermann, Sachs-Georgi, and Kahn reactions in the blood were negative. Basal metabolic rate - 12.5 per cent.

A diagnosis was made of hypofunction of the anterior lobe of the pituitary, possibly due to the presence of a tumour. This was based on the characteristic facies, the loss of the pubic and axillary hair, the diminished libido, the decalcification of the skeleton, and the low basal metabolic rate. A diagnosis of subacute combined degeneration of the cord was based on the subjective sensation of tingling in the legs, the absence of the ankle-jerks, the right-sided extensor plantar response, and the gastric achylia.

Confirmation of the diagnosis of hypofunction of the anterior lobe of the pituitary was provided by the results of treatment with a preparation of the anterior lobe of the pituitary containing thyrotropic and gonadotropic hormones. After ten daily injections the patient's basal metabolic rate had increased from - 12.5 to + 13.5; he was more lively, his facial expression and the movements of his joints had become nearly normal. He ceased to complain of chilliness and could walk more easily. The growth of his beard increased.

The blood-pressure remained high, the systolic varying between 210 and 180 mm. of mercury and the diastolic between 120 and 80 mm. The blood count was almost the same as in 1935: red cells 4,000,000 per c.mm., haemoglobin 75 per cent., leucocytes 7,400 per c.mm. Differential count: polymorphonuclears 51 per cent., lymphocytes 37 per cent., and eosinophils 11 per cent. Mean corpuscular volume 63 cu. μ .

Summary. The case is described of a man of 58 years of age with symptoms and signs attributable to hypofunction of the anterior lobe of the pituitary, complete gastric achylia, and a mild hypochromic anaemia, who

developed signs of subacute combined degeneration of the cord. The results of treatment with a preparation of thyrotropic and gonadotropic hormones lends support to the original diagnosis.

Case 5. H. W., male, aged 57, was admitted in January 1935, to the London Hospital (Reg. No. 30016/1935).

History. Worked in a rubber factory for thirty-three years, and from 1926 to 1932 as a sand-blaster. No work since 1932. Small-pox aged 8. 'Nervous breakdowns' at age 33 and 47; he was in a hospital for several months on each occasion. He had always lived in London; had always been undersized; had feeble erections from age of 18 to 54; never had intercourse and was unmarried. He had never shaved more often than once in several months. His father and adult brother shaved daily. He complained of nothing but constipation till at the age of 55 he began to have attacks of colicky abdominal pain and diarrhoea, never with any blood in the motions. Five months before his first admission his face became 'yellow' and he became increasingly breathless on exertion. At the time of admission he was passing eight to twelve motions a day, mostly in the morning. He had lost weight (9 st. 4 lb. as a young man). Never bleeding or tetany.

Physical condition (January 1935). Height 5 ft. 1 in., weight 6 st. 8 lb. Temperature from 97° to 97.5° F. An undersized man, effeminate and mentally childish but friendly and co-operative. Extremely pale, with a lemon-yellow tint of the skin and conjunctivae. Tongue normal. Voice high pitched and piping. Skin of smooth delicate texture. No axillary hair; scanty pubic hair of female distribution; soft down only on upper lip. Infantile genitalia; penis 3½ inches long and 2½ inches in circumference. No testes palpable in scrotum or inguinal canals. Lower dorsal kyphosis with corresponding horizontal crease in abdominal wall. Slight genu valgum. Partial webbing of both ring and middle fingers and both second and third toes. Chvostek and Trousseau signs negative. Examination of the heart and chest showed no abnormality. Blood-pressure 110/70 mm. of mercury, on admission, and 150/80 mm. on discharge. Spleen not felt. Prostate small. Nervous system, fundi and visual fields normal.

Investigation. Blood count: red cells 1,550,000 per c.mm., haemoglobin (Haldane) 36 per cent., colour index 1.16, leucocytes 1,330 per c.mm. Differential count: polymorphonuclears 58 per cent., lymphocytes 41 per cent., large hyalines 1 per cent. Stained films showed anisocytosis, poikilocytosis, and megalocytosis. Reticulocytes 0.4 per cent. Mean corpuscular diameter (Price-Jones method) 7.95 μ , σ 1.0052, megalocytosis 23.2 per cent. Mean corpuscular volume 116 cu. μ . Van den Bergh reaction; direct negative, indirect 0.75 units. Blood urea 36 mg. per 100 c.c. Serum calcium 8.7 mg. per 100 c.c., plasma phosphorus 2.4 mg. per 100 c.c., plasma phosphatase 0.17. Wassermann reaction in blood negative. Urine normal; no Bence-Jones protein. Stools: total fat 32.8 per cent., split fat 16.1 per cent by weight of dried stool. Sugar tolerance test normal. Calcium balance: mean of two three-day periods on low calcium diet, intake 0.306 grm., output 0.99 grm. (urine 0.29 grm., faeces 0.70 grm.). Radiograms of bones with normal control showed moderate generalized osteoporosis. Sella normal. Calcification in thoracic aorta and arteries of pelvis. Opaque enema showed no abnormality.

The patient was treated with adequate doses of a potent liver preparation given by intramuscular injection. The reticulocyte count rose rapidly from

the fourth day of treatment to reach a maximum of 15.5 per cent. (considerably less than the expected maximum) on the eighth day. At the end of five weeks the haemoglobin percentage was stationary and iron was administered. At the end of six weeks the red-cell count was 5,100,000 per c.mm. and the haemoglobin 80 per cent. The clinical condition was much improved, but the infantilism remained unchanged.

After discharge from hospital, treatment with iron and weekly injections of a liver preparation were continued for three months until April 1935, when the blood count was red cells 5,120,000 per c.mm., haemoglobin 92 per cent., colour index 0.92, leucocytes 4,550 per c.mm. The patient was then not seen until January 1936, when in spite of the absence of treatment for eight months his blood count was red cells 4,330,000 per c.mm., haemoglobin (Haldane) 96 per cent., colour index 1.1, leucocytes 6,600 per c.mm. He was treated with iron only until May 1936, when he was readmitted for further investigation. Since the time of the previous admission he had been lacking in energy, and had suffered from occasional attacks of giddiness and mistiness of vision. He had no diarrhoea.

Physical examination (May 1936). Weight 8 st. 3 lb. He had developed considerable amounts of subcutaneous fat, particularly over the buttocks, abdomen, and breasts (Fig. 3). Temperature almost constantly 97° F. No evidence of anaemia. Physical condition otherwise unchanged. Blood-pressure 170/95 mm. of mercury.

Investigation. Blood count: red cells 4,480,000 per c.mm., haemoglobin (Haldane) 98 per cent., colour index 1.02, leucocytes 2,700 per c.mm. Differential count: polymorphonuclears 54 per cent., eosinophils 9 per cent., lymphocytes 28 per cent., large mononuclears 8 per cent. Stained films showed no poikilocytosis or excess of anisocytosis. Reticulocytes 0.7 per cent. Mean corpuscular diameter (Price-Jones method) 7.73μ , σ 0.5350, megalocytosis 3.6 per cent. Van den Bergh reaction normal. Fractional test meal with histamine showed complete achlorhydria. The basal metabolic rate determined on five occasions before treatment varied from -9 to -17 per cent. The administration of 1 c.c. of thyrotropic hormone (Collip) subcutaneously daily for four days produced a sharp rise to +124 per cent. on the fifth day, followed by an equally rapid fall to -20 per cent. two days later. Increase of dosage to 2 c.c. for five days and then to 4 c.c. for one day produced a further small rise of basal metabolic rate to +32 per cent.

Apart from the production of some degree of excitement, this treatment had no noticeable effect on the patient's condition, except that the blood-pressure which before treatment was 170/95 mm. of mercury was found on the eleventh day of the administration to be 170/130 mm., on the eighteenth day to be 200/130 mm., and on the nineteenth and last day to be 235/135 mm. Four days later it was 170/135 mm., and five and eight weeks later it was 160/110 mm. and 200/110 mm. respectively.

The patient's general condition has remained unaltered. He has been treated with pil. ferri 6 grm. daily, and his blood count two months after discharge from hospital was red cells 4,520,000 per c.mm.; haemoglobin 96.0 per cent.; colour index 1.06; leucocytes 9,330 per c.mm. He has had no diarrhoea since he was first admitted.

Summary. The case is described of a man of 57 with infantilism, probably due to hypofunction of the anterior lobe of the pituitary, who developed complete gastric achylia and a megalocytic hyperchromic anaemia,

which responded to treatment with injections of liver extract. Support for the original diagnosis was provided by the result of treatment with thyrotropic hormone on the basal metabolism.

Case 6. E. T., male aged 44, was admitted on May 14, 1935, to St. Bartholomew's Hospital, complaining of anaemia.

History. At the age of 13 he began work at a coal mine and was strong and healthy until he was 18, when he was in a hospital for three months with diarrhoea and vomiting. He apparently recovered completely, joined the army in the War, and was passed A 1. After three months in France he developed dysentery, suffering much abdominal pain with diarrhoea and the passage of blood and slime. Six months later his dysentery was better but he then had neurasthenia for which he was treated for another year in a hospital for neurasthenics. About this time he began to have severe epigastric pain and vomiting, and soon he could keep nothing down. An abdominal operation was performed of which no details are available, but no gross abnormality appears to have been found. He was discharged from the army with a pension.

He continued to have attacks of severe dyspepsia, with pain soon after meals relieved by vomiting. He was constipated and often passed bright red blood with his motions. He lived on a meat-free diet. In 1923, when he was 31 years old, he was readmitted to a military hospital and a second operation was performed on account of his dyspepsia. The appendix was removed, and as the duodenum was very large in its upper two-thirds, suggesting some slight obstruction below the superior mesenteric artery, duodeno-jejunostomy was performed. He still suffered from dyspepsia off and on. His bowels were no longer confined but loose, because he took four vegetable laxative pills a day. He continued to lose blood per rectum and the pan was always streaked with blood. He had no other haemorrhage. During the last six years he had become very pale, much more so during the last three years. For one year he had taken a preparation of liver but he had not had iron. He lived on a fish and egg diet, and he had done no work since the War. He came of a healthy stock, having two brothers and six sisters who were all alive and well, and there was no family history of anaemia or endocrine disturbance.

Apart from the dyspepsia, the chief symptoms were those of anaemia. He was breathless on the smallest exertion, with palpitation, a sense of constriction in the throat, and at times gripping precordial pain. He had never had a sore tongue or dysphagia. There were no paraesthesiae or cramps. He was unmarried and had no interest in women. He had become very slow, easy-going, and lethargic and lived a purely vegetative existence.

Physical condition (May 1935). Height 5 ft. 6 in., weight 9 st. 1 lb. The patient had advanced frontal and occipital alopecia, with complete absence of hair of the eyebrows and the axillae (Plate 6, Fig. 4). His face was smooth and hairless, and he shaved infrequently at intervals of several weeks. There was scanty pubic hair, but the penis and testes were of normal size. Although he was lethargic, there was no resemblance to myxoedema, the skin being smooth and soft, and the subcutaneous tissues appearing normal. Apart from pallor, a systolic murmur over the precordium and haemorrhoids, physical examination revealed no abnormality. Blood-pressure 134/80 mm. mercury. The visual fields were normal and there were no symptoms or signs of disease of the nervous system.

Investigation. Radiograms of the skull showed no abnormality. Examination of the stomach showed achlorhydria which persisted after the injection of histamine. The stools were completely digested and contained no occult blood, ova, or parasites. Radiographic examination of the alimentary tract was normal except for slight intestinal hurry. The gastro-scope revealed a diffuse pan-gastritis of a mild type, the folds being smaller and less regular than normal and the colour of the mucosa being paler. The Wassermann and van den Bergh reactions were negative. The basal metabolic rate was -29 per cent., the blood cholesterol was 138 mg. per 100 c.c. The blood count was red cells 2,800,000 per c.mm. haemoglobin 30 per cent., colour index 0.5, reticulocytes 2.6 per cent., white cells 5,100 per c.mm., differential white count normal.

Under treatment with iron his haemoglobin rose steadily, and on July 17, 1935, he had 4,960,000 red cells per c.mm., and 87 per cent. haemoglobin. In spite of repair of the anaemia and improvement in the general condition, the basal metabolic rate remained low, fluctuating between -20 and -30 per cent. Treatment with thyrotropic hormone of the pituitary gland was begun on July 19, 1935, and he received a total of 6,000 units in six daily injections. The metabolism rose steeply, reaching a peak of +88 per cent., on August 9, 1935. There was a suspicion of swelling of the thyroid gland, and the patient became much more active. By August 19, 1935, the metabolic rate had fallen to +14 per cent. His haemorrhoids were treated by injection and he was discharged from hospital much improved.

The patient has been seen at intervals and he maintains his improvement. His last blood count at the end of April 1936 showed 4,170,000 red cells, 80 per cent. haemoglobin, and 5,250 white cells per c.mm. His basal metabolic rate has tended to fall, being -3 per cent. in November 1935, +16 per cent. in March 1936, and -16 per cent. in May 1936. His achlorhydria has remained refractory to histamine and there has been no growth of hair on the face or the axillae.

Summary. The case is described of a man of 34 years of age with signs attributable to an insufficiency of the anterior lobe of the pituitary, who developed gastric achlorhydria and a hypochromic anaemia. The anaemia reacted to treatment with iron, and support for the original diagnosis was provided by the effect of treatment with thyrotropic hormone on the basal metabolism.

Discussion

The symptoms presented by these six patients were so strikingly alike as to justify their inclusion in a single syndrome. One of them had signs of a chromophobe adenoma of the pituitary gland, while the other five had symptoms which pointed clearly to insufficiency of the anterior lobe of the pituitary. Four were males and two females. They came under observation at ages varying from 42 to 58, but in several symptoms had been present for a number of years, and in the two men with imperfect descent of the testes a lesion had obviously existed since the beginning of life. Insufficiency of the gonads was shown by lack of physical vigour and sexual interest or desire, amenorrhoea, and in two cases small size and imperfect descent of the testes. The hypogonadism appeared to be of the secondary

or pituitary type. The facies was dull and expressionless, the movements lethargic, sexual hair was absent, and the hair on the scalp and eyebrows was scanty or absent. The basal metabolic rate was not tested in the woman with the chromophobe adenoma. Of the other cases, it was reduced in four, while the fifth had taken thyroid. Four of the patients were treated with the thyrotropic hormone of the anterior lobe of the pituitary gland; three responded with a considerable increase in metabolism, and in the third case, which did not respond, there was reason to doubt the activity of the extract. There was no reason to believe that the patients were suffering from true myxoedema. The skin was soft, moist, and elastic, there was no infiltration of the subcutaneous tissues, and their appearance bore no resemblance to myxoedema. Moreover, the depressed metabolism of myxoedema is not raised by thyrotropic hormone (Scowen, 1937).

All the patients had hypochlorhydria, and five had complete achlorhydria. Anaemia developed relatively late in the course of the disease. In three there were symptoms of subacute combined degeneration of the spinal cord; in one the anaemia was hypochromic and responded to iron, and in two it was of the Addisonian type and responded to liver. The responses were prompt and were attended by reticulocyte reactions, and it is therefore manifest that the anaemia was a deficiency dyshaemopoiesis. It was essentially a gastrogenous anaemia, but at present we can do no more than speculate on possible connexions between the gastric and the endocrine defect. Achlorhydria is unduly frequent in a variety of endocrine disorders. The gastric secretion is diminished in pregnancy and in B-avitaminosis, and in both of these conditions the activity of the anterior lobe of the pituitary gland is depressed. Dodds and his collaborators (1934, 1935) have shown that injections in animals of a special preparation from the *posterior* lobe of the pituitary may produce severe changes in the acid-forming portion of the stomach and a profound anaemia. It is difficult to link their experimental results with our clinical observations on the association of anaemia and achlorhydria with defective function of the *anterior* lobe of the gland.

The relationship between the pituitary and haemopoiesis is a complicated one. Changes in the blood count can be produced by lesions of the pituitary or hypothalamus through mechanisms other than a direct endocrine effect on haemopoiesis. Alteration in the water balance of the body, which is known to be affected by centres in this region, can lead to an apparent polycythaemia or anaemia. An analogous example of such an apparent polycythaemia is that due to dehydration in Addison's disease. In pituitary lesions, showing changes in the blood count, these causes must be excluded before the question of an endocrine effect on haemopoiesis can be considered. In reported cases of polycythaemia associated with encephalitis, concussion of the brain, tumours of the third ventricle, and Huntington's chorea, these exclusions do not appear to have been made. The same criticism applies to some of the reported cases of polycythaemia associated with pituitary

basophilism, which has been used as a main argument for the theory of a pituitary influence on haemopoiesis. In any case, polycythaemia in this syndrome has been an infrequent occurrence (Russell, Evans, and Crooke, 1934). The clinical evidence so far adduced for a direct pituitary effect on haemopoiesis is inconclusive.

We believe that our cases illustrate an indirect effect of the pituitary on haemopoiesis. They appear to show that insufficiency of the anterior lobe of the pituitary may be followed by achlorhydria, and that this achlorhydria may induce after a long interval an iron deficiency anaemia, a liver deficiency anaemia, subacute combined degeneration of the cord, or a combination of these conditions. It is probable that anaemia only occurs after achlorhydria has been present for a considerable period, and that this explains the absence of anaemia in Simmonds's disease, which is of short duration, so that there is not time for achlorhydria to induce an anaemia. The suggested mechanism is very similar to that which has been offered to explain certain types of anaemia found in myxoedema. Achlorhydria is more common in patients with myxoedema than in normal persons, and of patients with myxoedema anaemia is more common in those with achlorhydria than in those with a normal gastric acidity (Lerman and Means, 1932). The anaemia may be a hypochromic one, resembling iron deficiency anaemia; very occasionally a hyperchromic Addisonian one, and sometimes a hyperchromic megalocytic one quite unlike Addisonian anaemia, which does not react to liver, but does react slowly to thyroid alone (Mackenzie, 1926; Means, Lerman, and Castle, 1931; Holbøll, 1935, 1936; Bomford, 1936). Bomford has suggested that the last type is to be regarded not as a deficiency dyshaemopoietic anaemia, but as an atrophy of the erythron secondary to the diminished needs of the myxoedematous subject for oxygen; whereas in the case of the hypochromic and Addisonian hyperchromic types achlorhydria has led to dyshaemopoiesis due to iron or liver deficiency. The mechanism that we have suggested to explain the occurrence of anaemia in our cases of pituitary dysfunction, is therefore essentially the same as that which has been invoked to explain certain types of anaemia found in association with myxoedema.

It is possible that our observations explain the remarkable syndrome called 'pseudo-tabes pituitaria'. Sternberg in 1897 drew attention to the fact that now and then, in cases of acromegaly, symptoms of tabes dorsalis are found. The observations of Sternberg and others, made in a period when Wassermann reactions and X-rays of the sella turcica were still unknown, cannot stand the test of modern criticism. In 1914, however, Oppenheim emphasized the fact that pseudo-tabetic symptoms may be present in affections of the hypophysis. He described three cases of this combination, consisting of—

- (1) bilateral atrophy of the optic nerves;
- (2) impotence and disappearance of libido;
- (3) reduction of knee- and ankle-jerks.

In modern literature some analogous observations can be found, though the total number is small (Needles, 1934; Otto, 1936).

The explanation of the pseudo-tabetic symptoms, which may accompany diseases of the hypophysis, has always been difficult. Increased intracranial pressure can damage the cord, but this cannot be the explanation of pituitary pseudo-tabes, for in several cases the pressure of the cerebrospinal fluid has been determined and found normal. In 1933 Dr. Biemond, consulting neurologist to the Wilhelmina-Gasthuis, Amsterdam, discussed the possibility that Case 3 might be considered a case of pituitary pseudo-tabes. He referred to this patient in a formal discussion and made the remark that perhaps the neurological symptoms in pernicious anaemia might be caused by endocrine disturbances. The achlorhydria, found in our cases of dysfunction of the anterior lobe of the hypophysis, throws a new light on the problem of pituitary pseudo-tabes. Probably many cases of this disease should be considered as a combined sclerosis due to gastric achylia. Symptoms of sclerosis of the cord in diseases of the anterior lobe of the hypophysis are relatively infrequent, because gastric achylia may be present for a long time before pernicious anaemia or disease of the cord develops. Thus, even if gastric achylia was a frequent or constant concomitant of special affections of the anterior lobe of the hypophysis, symptoms of anaemia or spinal disease caused by the achylia might still be rare.

Summary

1. Six cases are described of a syndrome characterized by hypogonadism, alopecia, depression of metabolism, and anaemia, apparently due to a lesion of the anterior lobe of the hypophysis.

2. Five of the patients had achlorhydria. It is concluded that the anaemia was not the immediate effect of pituitary deficiency, but was produced indirectly, and as a result of the achlorhydria.

3. It is suggested that the condition described as pituitary pseudo-tabes is an allied syndrome, due to the association of pituitary disease, achlorhydria, and subacute combined degeneration.

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DESCRIPTION OF PLATE

FIG. 1, Case 1. Hypopituitarism and hypogonadism with development of pernicious anaemia. Note disappearance of all facial hair and of most of the hair of the scalp.

FIG. 2, Case 2. Hypopituitarism with gastric achylia and hyperchromic anaemia. Basal metabolism—30 per cent. Thin face, completely different from the 'moon face' found in cases of myxoedema.

FIG. 3, Case 5. Hypogonadism due to hypofunction of the anterior lobe of the pituitary, with development of Addisonian hyperchromic anaemia.

FIG. 4a and b, Case 6. Advanced frontal and occipital alopecia in a man with hypofunction of the anterior lobe of the pituitary, who developed a hypochromic anaemia.

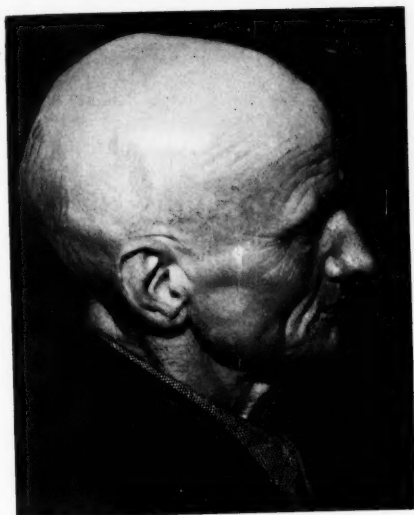


FIG. 1



FIG. 2

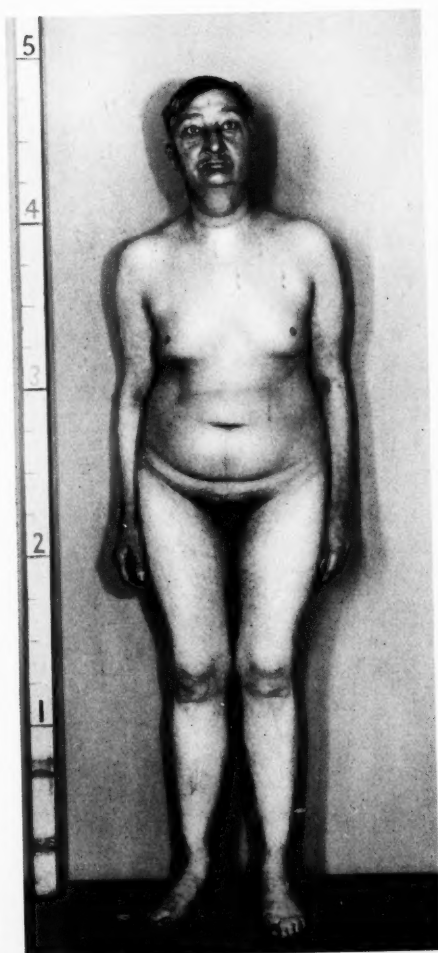


FIG. 3

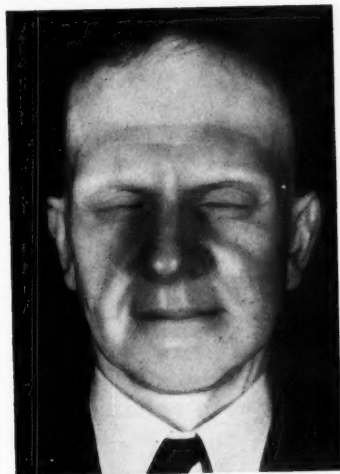


FIG. 4 a

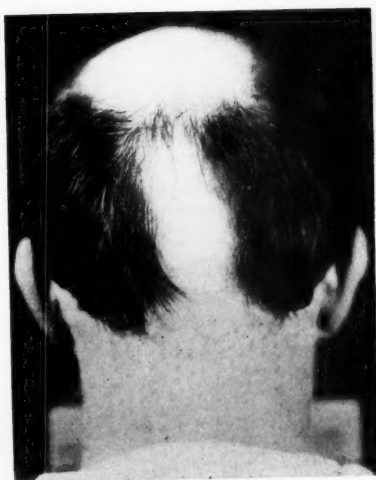
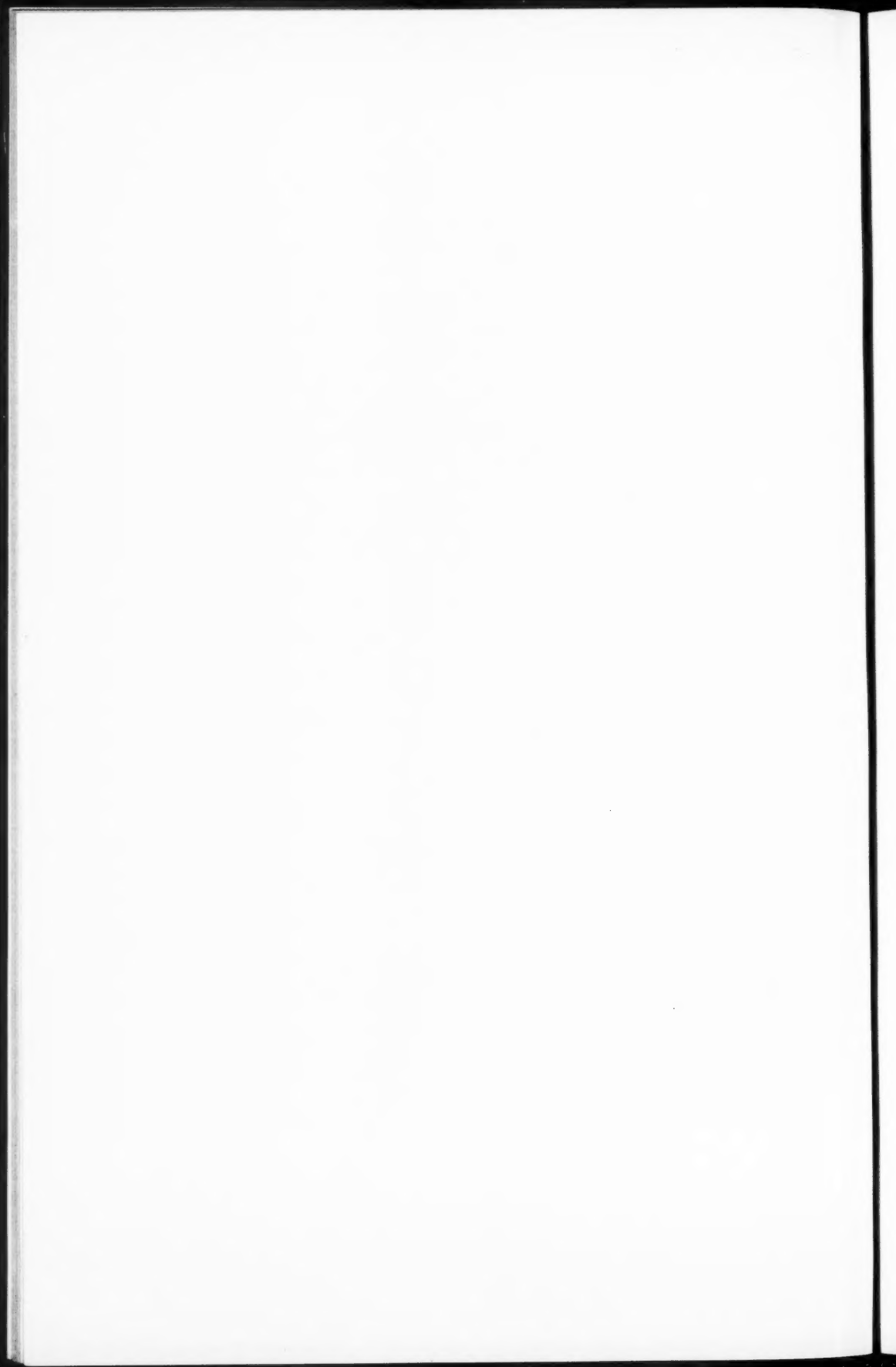


FIG. 4 b



PLASMA PHOSPHATASE IN DISEASE: A REVIEW¹

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In 1923 Robison (72) demonstrated in the bones of young rats an enzyme which had the power of hydrolysing calcium hexosemonophosphate, an organic acid-soluble phosphorus compound. This enzyme, phosphoric esterase or phosphatase, has also been found in kidney, intestinal mucosa, muscle, and other tissue. Robison's work stimulated interest in the distribution and significance of phosphatase in view of the importance of its action in the metabolism of lime and phosphorus. It was soon shown that its presence in any tissue depended on the functional activity of the cells: thus no evidence of phosphatase is obtained in foetal kidney, while in cartilage it does not make its appearance prior to the commencement of ossification (56). Martland and Robison (56) concluded that the production of the enzyme is an essential part of the cellular activity of ossifying cartilage. This view is supported by the finding of Wilkins and Regen (83) that irradiation of one foreleg in puppies delayed increase in weight and length and led to a reduction of plasma phosphatase presumably because of diminished cellular activity.

The problem of the identity of the phosphatases found in the various tissues has been dealt with by Kay in a comprehensive review of phosphatase activity in general (48 *b:c*). At first it was thought that all tissue phosphatases with the exception of that found in the red cells were identical. Later work has given evidence, however, that several varieties of phosphatase exist in the animal body, although absolute specificity, if it exists at all, must be very rare.

Phosphatase activity was first demonstrated in the blood-plasma by Martland, Hansman, and Robison (55). Although the leucocytes are rich in phosphatase (74) (82), its presence in the plasma is probably in very large part due to its passage from the tissues. Roche (75) found that plasma phosphatase closely resembled that obtained from kidney and intestinal mucosa in the optimum physico-chemical condition of activity. The amount of enzyme in the plasma is often taken as a rough estimate of its production in the tissues, but it is quite possible that an increase in plasma phosphatase may, at times, be due to the fact that less is being utilized in its place of origin.

¹ Received January 30, 1937.

Phosphatase acts on the phosphoric esters which are formed in the course of catabolism of carbohydrates (hexosephosphate), fat (glycerophosphate), and nucleo-protein (nucleotide). As a result of this action free phosphorus is liberated with the consequent increase of inorganic phosphate. Thus it plays an important part in ossification leading to the deposition of calcium phosphate, in carbohydrate metabolism, in the urinary excretion of phosphate and indirectly in the maintenance of acid-base equilibrium and the chemical changes taking place during muscle activity.

Estimation of plasma phosphatase. The value of the plasma phosphatase is determined by estimating the amount of inorganic phosphate which can be formed from glycerophosphate or phenyl-phosphate by a measured amount of plasma during a fixed period of time at a fixed temperature. It is immaterial whether arterial or venous blood is used (66). Various times of incubation and methods of analysis have been used and the results are given in different units. It is necessary therefore to know the method employed before expressing an opinion as to the presence of any abnormality. Table I shows the maximum and minimum values obtained by the methods commonly in use.

Plasma phosphatase in health. Age has a significant influence on the level of the plasma phosphatase. Cantarow (22) using Bodansky's method reports that the phosphatase varied from 1.5 to 4.0 units in adults and 5 to 14.0 units in children. The increased value in children has been noted by other workers (41). It would appear that there is a tendency for plasma phosphatase to increase during periods when growth is marked. Stearns and Warweg (80) found that it was low at birth, rose rapidly to a maximum in the first month of life, remained at approximately this level during the first two years and thereafter gradually fell to within the adult range. An increase, however, has been noted between the ages of 10 and 15 (16) (66), possibly related to puberty and the increased activity of tissue cells concerned with growth. During pregnancy a high plasma phosphatase has been reported (25). Abstention from food for short periods does not appear to have any effect (22) but in rabbits after a seven-days' fast a reduction was found (66). Hyperglycaemia following the intravenous injection of glucose was accompanied by a fall in plasma phosphatase (66) but Bodansky (13) found that during alimentary hyperglycaemia there was a rise in phosphatase, while Freeman and Farmer (33) observed a decrease with high protein diets and an increase with diets rich in carbohydrate.

Exposure to the sun's rays led to an increase in plasma phosphatase proportional to the duration of the exposure (1). The administration of small doses of irradiated ergosterol also caused an increase, but toxic doses led to a reduction (33). Page and Reside (64), however, have shown that the decreased values for bone and other tissue phosphatase following large doses of irradiated ergosterol which were reported by Baumgartner et alii (9), are to be attributed to toxic by-products in the preparation used and not to vitamin D.

The Plasma Phosphatase in Pathological Conditions. A. Bone Disease

The work of Robison and his collaborators has shown that phosphatase produces an increase in the concentration of phosphate ions and thus brings about a deposition of calcium phosphate, a process which is obviously connected with the growth and nutrition of bone. It is therefore not surprising that most attention has been paid to changes in plasma phosphatase in bone disease. Of pathological conditions affecting the skeleton, Paget's disease and generalized osteitis fibro-cystica have been found to show the most marked increase in plasma phosphatase.

Osteitis deformans (Paget's disease). In 1929 Kay (47) found in seven cases of Paget's Disease an increase of plasma phosphatase of 4 to 20 times the normal average. He (48) thought that the increase in the plasma might be due to leakage from the bones where it had been produced in excess in order to compensate for the bony lesion, or might result from bending of the weakened bones which squeezed out some of the cellular contents. He further suggested that the continued leakage from the bone might be the cause of the irregular deposition of new bone outside the usual sites. Roberts (70) also found very high values for phosphatase in Paget's disease and, as in Kay's patients, the higher values occurred in the more advanced cases. Two of his patients were treated with various combinations of calcium salts, vitamin D, and parathyroid extract but without effect on either the plasma phosphatase or the clinical course of the disease. O'Reilly and Race (62) in 21 cases found that there was a rough correlation between plasma phosphatase and intensity of symptoms and X-ray findings. Bodansky and Jaffe (16) observed that the high phosphatase was greatly reduced when spontaneous healing by sclerosis occurred, and that Paget's disease localized to one or two bones, which was more frequent in patients over 60 years, was associated with a normal value or only a moderate increase of phosphatase. In a series of 20 cases Gutman and Gutman (35) found that in many the phosphatase level remained constant for over two years and that radiotherapy caused no change. These workers, after summarizing the findings of other writers, concluded that the level of the phosphatase reflects the rate of the development of the disease, being very much higher in patients in whom the disease was progressing rapidly than in those in whom it was clinically quiescent. Pautrat (66) also found that the height of the phosphatase was related to the activity and extent of the disease: in one patient in whom the disease had been quiescent for some years the value was within normal limits.

Plasma phosphatase is of little value in differential diagnosis, since it is increased in many other diseases of the bone. It may be useful in the early detection of skeletal abnormality before changes are seen on the skiagram, but its chief use will probably be in the estimation of the degree of activity of the disease.

Osteitis fibro-cystica. An increase of plasma phosphatase in osteitis fibrosa was first noted by Kay (47) and Hunter (44) in 1929. This was

followed by reports of more cases, in some of which the phosphatase reached values about twenty times the normal average (48). Cases have been reported by Keynes and Taylor (50), and Rankin and Priestley (69), while Landon (53) gave details of this condition occurring in a child of $2\frac{1}{2}$ years in whom the phosphatase was considerably increased. Page and Reside (65) found that in dogs, injection of parathyroid extract led to an increase of serum phosphatase. Bodansky and Jaffe (14) obtained similar results and Melanby (57) in 1932 stated that the increase of phosphatase was found only in the generalized form which is of course associated with hyperparathyroidism and not in the localized type. Albright, Aub, and Bauer (2) noted high values for phosphatase which fell to normal after removal of the parathyroid tumour: the rate of decrease appeared to run parallel with the process of calcification as estimated by skiagrams. Coryn (26) and Albright, Aub, and Bauer (2) maintain that osteitis fibro-cystica is always associated with high plasma phosphatase. The degree to which it is raised varies considerably in different cases. Thus Kay's (48) and Duvoir's (29) figures of 20 times normal may be contrasted with those of Quick and Hunsberger (68) who obtained a value only four times the normal in a patient with the clinical condition well marked, and of Austoni and Coggi (8) who reported only a slight increase in a patient with marked clinical manifestations but with normal values for serum calcium and phosphorus. Pautrat (66) reported the case of a patient who was not greatly benefited by removal of a parathyroid adenoma. Three years later the clinical manifestations were still well marked although the plasma phosphatase was less than twice the normal value: a second operation revealed the presence of neoplastic changes in the parathyroid tissue. Taylor (81) gives details of two patients, one with osteitis fibrosa associated with hyperparathyroidism and one with multiple bone cysts but no involvement of the parathyroid glands. In the first, the serum calcium was increased to 14.7 mg. per cent. while in the bones there was marked decalcification with giant cell tumours, and cysts: prior to treatment the phosphatase was about four times the normal value. After removal of the parathyroid tumour, serum calcium and phosphatase both fell to within normal limits and a negative calcium balance due to excessive loss in the urine became a positive one. In the second case there were multiple localized lesions in about 50 per cent. of the bones of the body: there was no evidence of parathyroid involvement, serum calcium and phosphorus being both low and the bulk of the output of calcium taking place by the faeces. The plasma phosphatase in this patient was increased to about three times the normal average. Elmslie (30) maintains that even in the presence of multiple bone cysts there is no increase in plasma phosphatase unless there is overactivity of parathyroid tissue. Our experience, however, indicates that in children multiple bone cysts, even when not due to hypersecretion of parathyroid hormone, may be associated with a slight, but only a slight, increase of plasma phosphatase.

Conditions of hyperparathyroidism generally lead to an increase in serum

calcium and a reduction in serum phosphorus. Albright et alii (3), however, have pointed out that neither hypercalcaemia nor hypophosphataemia may be present if real renal function is impaired, a condition which may very well occur as a result of calcium deposition in the kidney. In such a case the only positive biochemical evidence of increased parathyroid activity is the high plasma phosphatase. On the other hand, Albright and his colleagues (2) in another communication have reported three cases of hyperparathyroidism due to adenoma of parathyroid tissue but with neither increase of plasma phosphatase nor X-ray evidence of bone lesions. They point out that the degree of bone involvement is an index of the duration of the disease and not of its severity. One may therefore conclude that in hyperparathyroidism the increase in plasma phosphatase is proportional to the response of the bone cells. In these cases the serum calcium is high although the phosphatase is within normal limits. The routine determination of plasma phosphatase and serum calcium and phosphorus is therefore advisable.

Generally it may be said that in the presence of bone lesions suggestive of hyperparathyroidism a great increase in plasma phosphatase may be of considerable value in determining whether or not there is over production of the parathyroid hormone and therefore whether operative interference is required. The association of high plasma phosphatase and low serum calcium strongly suggests the presence of some renal complication, especially if serum phosphorus is increased. On the other hand, a high serum calcium should even with a normal value for phosphatase and in the absence of X-ray evidence raise the suspicion of early hyperparathyroidism.

Rickets. In 1925 Demuth (28) obtained high values for plasma phosphatase in rickets. Later Kay (48) found that in various types of human rickets (infantile, adolescent, and renal) the plasma phosphatase was increased in value from four to twenty times the normal average. In a general way he thought the increase was correlated with the severity of the disease. Roberts (70) also obtained increased values in adolescent human rickets as well as in experimental rickets in the dog, but found that there was no increase when the rickets was healed. Mellanby (57), too, stated that the phosphatase was normal in subjects with healed rickets. Smith and Maizels (78) carried out serial estimations of the plasma phosphatase in children with active rickets while antirachitic therapy was being administered. At the commencement of the investigation the phosphatase had reached a value about two and a half times the normal average; this was found to decrease gradually, arriving within normal limits only when healing was complete. Stearns and Warweg (80), however, found that the plasma phosphatase was still above normal limits, even when the skiagrams showed that the rachitic process had healed. Careddu and Brigenti (23) reported values which, although above normal, were not as high as those obtained in rickets by other workers: a reduction was noted after ultra-violet irradiation. An interesting point was the fact that while in health the bulk of the

phosphatase was a hexosediphosphatase, in rickets glycerodiphosphatase preponderated. Bodansky and Jaffe (17) investigated the relationship between the height of the plasma phosphatase and the severity of the rachitic condition and the rate of healing. The method employed by these workers differed from that of Smith and Maizels (78), but their rachitic patients showed a relatively very much greater increase over normal values than did those of the other investigators. This they attributed to the fact that their patients were negro children on whom exposure to sunlight would have less prophylactic effect than on white children, and possibly also because at the time of the investigation there was a severe economic depression with consequent dietary restrictions. They found that the phosphatase value showed a rapid and continuous decline after the commencement of cod liver oil administration. In some patients a normal value was reached, but in others the phosphatase became stabilized above the high normal level. They concluded that a normal value is not obtained until the reconstruction of the affected bones is completed. The phosphatase was also determined in some cases before treatment was commenced: in these the values continued to rise. Interruption of treatment, the duration of the interruption not being stated, was also followed by a rise in phosphatase and a fall in serum phosphorus. Bodansky and Jaffe (17) state that the stabilization of phosphatase, even at a high value, is of more importance than the actual figure obtained, since the stabilized value is reached while healing is taking place although not actually complete, and indicates that an adequate dose of antirachitic factor is being given. Andersen (4) on the whole obtained very similar results. In some of his patients the phosphatase fell to within normal limits in one month, while in others three months were required. He found, however, that in some patients clinical improvement was marked before the phosphatase began to fall. Morris et alii (59) in an attempt to assess the value of plasma phosphatase as a diagnostic test for rickets, and as a means of determining the presence and rate of healing, analysed the results obtained from the examination of 506 infants and children in the first two years of life, who either had manifest rickets or might possibly have been suffering from the effects of vitamin D insufficiency. In 84.1 per cent. of the cases with clinical or radiographic evidence of rickets, the plasma phosphatase was increased above normal limits. The fact that in some cases with radiographic signs of rickets the plasma phosphatase was not increased, makes it obvious that a normal phosphatase value cannot be taken as infallible evidence of the absence of rickets. On the other hand, 101 patients had an increased value for phosphatase without either clinical or radiographic signs of rickets, although 59 of these had low values for the serum phosphorus or calcium-phosphorus product. This suggests that a high phosphatase in a child of an age prone to rickets and without other bone disease is, even in the absence of clinical or radiographic evidence, indicative of a very early rachitic state. This view is supported by the findings of Smith (77) and Pautrat (66), that an increase in plasma phosphatase is the

most sensitive indicator of an active rachitic process in infants. Furthermore, Auchinachie and Elmslie (7) have shown that in sheep fed on a low calcium diet, the rise of plasma phosphatase gave a much earlier indication of disordered metabolism than either serum calcium or blood inorganic phosphorus or general state of health. A rough parallelism was observed between the height of the phosphatase and the severity of the rachitic process, but some cases with very mild rickets were found to have a much higher phosphatase than other patients with more marked signs of rickets. Thus the level of the phosphatase cannot be taken as an index of the severity of the disease in the individual patient. In untreated active rickets the plasma phosphatase continued to rise. The initial stage of healing was generally accompanied by a stationary value for the phosphatase, but in a few cases a transient small but definite rise was noted shortly after the initiation of vitamin D therapy. The fall of phosphatase in every case occurred after the appearance of signs of healing on the skiagrams, so that unless a stationary value is taken as evidence of healing, determination of the plasma phosphatase is not more efficient than skiagrams in detecting the early stages of recovery. The rate of fall of the phosphatase to normal limits appeared to depend on the dosage of vitamin D. Moderate doses did not produce a return to normal within several months, while large doses achieved this in five weeks.

In both coeliac and renal rickets the plasma phosphatase is increased.

It would appear, therefore, from a consideration of the findings of these various investigations, that the determination of plasma phosphatase, while it has a place in the diagnosis of the preclinical stage of the disease, cannot by itself be used to indicate the severity of the rachitic process or the presence or absence of healing.

Osteomalacia. Kay (48), in a patient aged 21 years with osteomalacia, found that the plasma phosphatase was increased about 10 times above the normal average. Administration of a high calcium diet with viosterol resulted in great clinical improvement associated with a marked diminution in the phosphatase. A high value for phosphatase was also observed in another patient in whom the condition was complicated by the presence of rachitic deformities. Pautrat (66) has also reported a case in which the phosphatase was increased, but only to a slight extent. In the U.S.A. osteomalacia is practically limited to conditions associated with fatty diarrhoea which leads to a great reduction of calcium retention. In such cases both Bodansky and Jaffe (16), and Albright, Aub, and Bauer (2) have reported increased values for plasma phosphatase. Although the available data are scanty, it would appear that in osteomalacia, however produced, there is, as in rickets, an increased amount of phosphatase in the plasma.

Osteogenesis imperfecta. Kay (48) found that in this condition there was a tendency to a raised value, but not always an increase in plasma phosphatase. Bodansky and Jaffe (16), however, felt that the increased values reported by Kay might well be due to normal variations. Kersley (49)

found that plasma phosphatase was increased in children with this condition, but was within normal limits in adult patients.

Smith and Mitchell (79) collected a series of 22 uncomplicated cases of osteogenesis imperfecta: in eight an increase of plasma phosphatase to about twice the normal average was observed, but in the remaining 14 they found no abnormality in the phosphatase level. Our own results are similar; in a few cases a slight increase was found. Hansen (38), while obtaining approximately normal values for plasma phosphatase, found that the ferment was entirely absent from the periosteum and subperiosteal tissue. The lack of phosphatase in these structures, which are normally rich in this enzyme, probably accounts for the defective calcification of the cortex of the bone. In one patient who died suddenly, Hansen and Ziegler (39) observed a relative increase in the phosphatase activity of the callus, suggesting a temporary mobilization at the site of injury. Hansen (38) also reported that the duodenal mucosa, which usually has a high content of phosphatase, is poor in this ferment in cases of osteogenesis imperfecta, and suggested that this may account for the low retention of phosphorus noted by some workers.

Osteoporotic conditions. In generalized osteoporosis, phosphatase is slightly increased in young and middle-aged patients, but not in the old (37). It would appear that the bone cells in elderly subjects tend to lose their vitality, and therefore their capacity to increase their phosphatase production. In the osteoporosis associated with non-tropical sprue there is a slight rise in plasma phosphatase and a reduction of serum phosphorus (16). In experimental decalcification produced by calcium deficiency, Bodansky, Jaffe, and Chandler (19) found a rise in serum phosphatase. We have observed the same phenomenon in a patient who was kept on a calcium-poor diet in order to soften the bones. When ammonium chloride was given to children we found that there was either a slight rise or a slight fall in the plasma phosphatase, whereas Bodansky, Jaffe, and Chandler (19) observed only a rise. In the demineralization which frequently accompanies hyperthyroidism, the phosphatase is generally increased (16, 22). It is interesting to note that after complete section of the nerves supplying individual bones, there occurs, together with decalcification, a marked reduction of the phosphatase activity of the affected tissue.

In five cases of uncomplicated osteoporosis circumscripta of the skull, Gutman et alii (36) found that there was little or no increase of plasma phosphatase, thus supporting Robison's view that a rise in plasma phosphatase in bone disease is an expression of the increase in the cellular activity leading to bone formation.

Osteopetrosis. In osteopetrosis (Albers Schönberg disease) plasma phosphatase is increased (16).

Fractures. Kay (48) and Roberts (70) found that fractures uncomplicated by any bone disease were associated with normal or but slightly increased values for the plasma phosphatase. In patients with early Paget's disease

who had sustained fractures, Roberts obtained values which did not differ much from normal. This is in accord with the observation of Bodansky and Jaffe (16), that osteotomy frequently leads to a decrease of previously high phosphatase in a patient with some disease process in the bones. They later suggest that the healing of the fracture counteracts the disease process. McKeown and Ostergren (54) state that phosphatase plays a part in the healing of fractures. Wilkins and Regen (83) observed a rapid increase of phosphatase at the site of fracture in adult rabbits, and synchronously with the greatest phosphatase activity at the site of fracture there occurred in some cases a slight increase of plasma phosphatase. Smith and Maizels (78), in six patients with fractures, found that the phosphatase, while normal immediately after the injury, increased about 10 days later, and remained high for some weeks, the height of the rise corresponding with the amount of callus laid down, and with the length of time before healing was complete. In Hunsberger and Ferguson's (43) series the phosphatase reached a maximum value in the third week after the injury, thereafter gradually falling to normal limits. Austoni and Coggi (8) found that the phosphatase value varied with the severity of the fracture. In rapidly healing slight fractures no rise was observed, while in multiple fractures of greater severity there was a slight increase, maximum values being obtained just prior to calcification of the callus. In a third group of but two cases with inter- and supra-condylar fractures of the femur, the plasma phosphatase increased immediately after the injury, and remained high until union occurred. Austoni and Coggi (8) believe that the rise in phosphatase depends either on the increased activity of the bone cells or on the destruction of osseous tissue. Mitchell (58) observed a slight increase in plasma phosphatase in many patients with fracture, but could not correlate the rise with either the degree or rate of healing. Botterel and King (20) found that out of a total of 26 patients with simple fractures that united, only three showed an increase of phosphatase. In two of the latter the rise was slight, and in one who had a fracture of the lower epiphysis of the femur, the level rose to two and a half times the normal average. In a group of four patients with fractures that did not unite, no significant increase of phosphatase was observed over a period of six weeks. Yaguda (86) could not find any relationship between the height of plasma phosphatase and the time that had elapsed since the fracture, but thought that highest figures were obtained in the severest injuries. In the few cases reported by Coryn (26) there was a slight increase in plasma phosphatase shortly after the injury, and a rapid return to normal limits. In our own series of patients with fractures, all below 12 years of age, a slight increase in plasma phosphatase was most frequently observed within the first few days: thereafter there was a decrease with a secondary rise about three weeks after the injury. The change in plasma phosphatase was most marked in fractures of the femur.

Bone infections. Koldajew and Altschuler (52) obtained definitely high values in cases of bone tuberculosis: in several instances the plasma

phosphatase was twice the normal value. They found that the rise was much less in the presence of a mixed infection, but that there was little parallelism between the extent and severity of the tubercular process and the height of the phosphatase. Similarly Murray (60) found that there was not a close relationship between the height of the plasma phosphatase and the degree of activity in bone and joint tuberculosis, although on the whole the values were lower in quiescent periods. It would appear therefore that the change in plasma phosphatase associated with tuberculosis of the bones is so slight as to be of little value either in the diagnosis or prognosis of the condition.

In osteomyelitis phosphatase values have been reported somewhat above normal (48). Pautrat (66) found that during the febrile stage there was no increase in plasma phosphatase even when the lesion was destructive, while a slight increase was observed in chronic conditions. In the few cases of this condition in children which we have examined, values which either fell within normal limits or only slightly exceeded them were obtained.

In syphilitic diseases of bone slightly increased values have been reported (29).

In patients with uncomplicated arthritis, plasma phosphatase fell within normal limits (86): in only three cases with local atrophy of the bone were high values obtained (16).

Neoplasm. In view of the fact that the production of phosphatase is a function of cellular activity, attention has naturally been paid to the possibility of variations in plasma phosphatase in malignant disease. Woodward et alii (85), however, found that in 13 cases of malignant neoplasm not involving either bone or liver, the plasma phosphatase was within normal limits. This has been the experience of most investigators (16), so that one may conclude that the production of phosphatase by non-osseous tumour cells is not sufficient to produce a significant increase of plasma phosphatase. With neoplasms affecting the bones different results have been obtained.

Coryn (26) found that in patients with cancer metastases in the bones the plasma phosphatase was increased, and Duvoir et alii (29) reported values about twice the normal average. Bodansky and Jaffe (16) obtained increased values in association with osteogenic sarcoma and metastatic carcinoma invading bone, but not with medullary sarcoma and malignant disease of tissues other than bone and liver. Simmons and Franseen (76) made observations on 72 patients with bone tumours of various types. They found that while the plasma phosphatase was within normal limits in cases of non-malignant tumours of bone, and occasionally very slightly increased in multiple myeloma, Ewing sarcoma, and giant cell tumour of bone, it was considerably elevated when carcinomatous metastases were present in bone, and consistently high in osteogenic sarcoma of the osteoblastic type. In the osteolytic type of osteogenic sarcoma, normal or moderately increased values were obtained (32, 37, 76). In Woodward's series of 14 cases (85) of malignant disease secondarily involving bone, the

phosphatase ranged from normal to about fifteen times this average, being highest when the primary tumour was carcinoma of the prostate. When the bone lesion was small, very slowly progressive, or chiefly osteolytic in nature, the phosphatase was little if at all increased, whereas widespread osteoplastic lesions were accompanied by high values. In 20 cases with benign bone tumours only one showed increase in phosphatase. According to Woodward et alii (85) the bone-forming characteristics of a tumour are of more importance than is its malignancy in determining a rise in phosphatase. They accordingly feel that the determination of phosphatase may be of value in differentiating a growing tumour with a high rate of osteoplastic activity such as osteogenic sarcoma, from a less rapidly ossifying tumour such as chondrosarcoma or a very slowly changing osteoma or old myositis ossificans all with similar skiagrams. Simmons and Franseen (76) found that after surgical removal of an osteogenic carcinoma the plasma phosphatase rapidly fell to normal only to increase again when metastases appeared. In this connexion it is to be noted that the metastasis attained an appreciable size before the increase in plasma phosphatase became marked. Radiation treatment of an osteogenic sarcoma caused in one case a temporary reduction of plasma phosphatase. Prior to death a great reduction in phosphatase activity was observed in several patients. Woodward et alii (85), however, state that the phosphatase is very variable after operation or treatment by Coley toxin or X-ray, and that serial determinations are without value in prognosis, and that even in the absence of complicating factors rise in phosphatase cannot be relied on to detect early metastases.

While the clinical and radiological manifestations, together with the excretion of Bence-Jones protein, make the diagnosis of myelomata easy, it is probable that in the early stages some of these signs are absent, and the condition may be confused with Paget's or Recklinghausen's diseases. In such a case the estimation of plasma phosphatase may be of considerable help in differential diagnosis. In a patient with multiple myelomata the plasma phosphatase is little, if at all, increased (16, 26, 86) in contradistinction to the high values obtained in the other two diseases.

Significance of increase in plasma phosphatase in bone disease. It is clear that the determination of plasma phosphatase by itself is of little value in either diagnosis or prognosis. Taken in conjunction with clinical, radiological, and other biochemical findings it may yield considerable assistance. The accompanying table (Table II), which has been compiled from various sources, gives a summary of data which may prove useful in diagnosis. In prognosis repeated estimations of plasma phosphatase will probably aid in the interim estimation of the efficiency of treatment in cases of Paget's disease, generalized fibro-cystic osteitis, osteogenic sarcoma.

The cause of the increase in plasma phosphatase is not yet decided. In the first place it may be stated that it is not due to some alteration in the constitution of the plasma (66) such as hypophosphataemia or excess of magnesium.

Kay (48) suggested that the increase in phosphatase activity of the plasma was due to excessive outflow of the ferment from the disturbed areas, either because of the mechanical damage to the bone cells produced by bending of the bone with resultant expression of cell contents or because of a compensatory overproduction of phosphatase. Duvoir et alii (29) hold the view that increase of phosphatase is an index of greater activity of bone cells and that this increase in cellular activity may be either osteoblastic or osteoclastic in nature. Bodansky and Jaffe (16) point out, however, that destruction of bone *per se* is not accompanied by a marked rise of plasma phosphatase unless there is also present some new formation of bone or osteoid tissue. Actually the phosphatase is highest when there is excessive formation of abnormal osseous tissue. They suggest that variations in plasma phosphatase may be due to variations in the cellular activities of the bone cells. These activities are said to be controlled by certain factors which operate in the normal development and growth of bone, and are probably altered when disease processes ensue. The deposition of normal osseous tissue would itself appear to be one of the factors limiting the activity of the bone cells. When anything occurs to prevent such a deposition, as in hypovitaminosis D, one of the controlling factors of cellular activity is absent, with the result that excess phosphatase is produced.

Some workers (77, 78), who have investigated the relationship of plasma phosphatase to rickets suggest that a high value is indicative of an insufficient supply of vitamin D since its administration is followed by a fall of the phosphatase to within normal limits. Smith and Maizels (78) have shown that withdrawal of vitamin D from the diet increases the phosphatase of the plasma without producing any clinical or radiographic signs of rickets, and we have observed in one child without any evidence of rickets that administration of vitamin D was followed by a fall in plasma phosphatase from its high level. But the fact that high values are obtained in Paget's disease and osteitis fibrosa precludes one from assuming that hypovitaminosis D is the essential factor in producing the phosphatase increase. On the other hand it has been shown by Smith that conditions characterized by diminished growth, such as cretinism, scurvy, and achondroplasia, are associated with low plasma phosphatase, while Bodansky and Jaffe (17) have found that in healthy children there is a tendency for plasma phosphatase to increase at periods when growth is most marked. Normally an increased amount of activity in the bone cells is accompanied by an increased rate of bone formation, and it seems reasonable to suggest that when the ossification for any reason does not increase *pari passu* with the increase in cellular activity and phosphatase formation, an excess of the ferment will pass over into the plasma with resulting rise in the plasma phosphatase value. In this connexion it is to be noted that the formation of osteoid tissue is an invariable accompaniment of a high plasma phosphatase. A discrepancy between bone cell activity and bone formation may arise in several ways.

(a) Increase in bone cell activity produced by hormone action. Thus it

has been noted that hyperthyroidism is generally accompanied by an increase in plasma phosphatase (16).

(b) Insufficient supply of minerals as a result of deficient intake.

(c) Defective utilization of minerals as in hypovitaminosis D.

In each of the last two conditions increases of plasma phosphatase have been reported. Where, however, a deficient supply of minerals exists together with diminished growth impulse as in coeliac disease, no increase of plasma phosphatase will ensue. Thus in coeliac disease the plasma phosphatase is only increased during a period when growth activity is resumed. It is probable that great diminution of growth activity is responsible for the normal values of plasma phosphatase in infants with radiological evidence of rickets.

It has been shown by Heymann (42) that the addition of parathyroid hormone *in vitro* to osseous tissue diminishes the activity of bone phosphatase; the same result was obtained by Page (63) on injecting parathormone into rats. Page and Reside (65) and Bodansky and Jaffe (14) found that injection of parathormone caused a rise in plasma phosphatase. Clearly this indicates, in the first place, that an increase in plasma phosphatase is not necessarily the result of an increased formation of bone phosphatase. Further, the rise in plasma phosphatase can reasonably be attributed to the fact that parathormone prevents its utilization at the site of production, with the result that an excess is carried over into the blood-stream. This would explain the increased plasma phosphatase in generalized osteitis fibro-cystica. In Paget's disease it is also possible that calcium is removed from osseous tissue at a quicker rate than it can be deposited, thus leaving active bone cells with insufficient calcium to satisfy their needs.

It would appear, therefore, that the factor which is finally responsible for the height of the plasma phosphatase in disturbance of bone metabolism is the relationship between cellular activity of the bone cells, the effective supply of lime and phosphorus and the ability of the cells to utilize these minerals. When either of the latter two is insufficient to meet the demands of the bone-forming cells the plasma phosphatase increases.

B. Non-osseous Conditions

Jaundice. In 1930 Roberts (70) reported a great increase in plasma phosphatase in two cases of obstructive jaundice with but a slight rise in one patient with catarrhal jaundice. In 1933 the same worker (71) reported a series of 52 cases of jaundice; in the 'obstructive' group the values for phosphatase varied between 10.9 and 22.9 with 9.4 in one patient who had slight jaundice, while in the 'haemolytic' group values were normal (2.2 to 5.5) and in the toxic-infective group figures varying between 3.7 and 9.4 were obtained. On the basis of these results Roberts concluded that the value for plasma phosphatase was of importance in differentiating between obstructive and non-obstructive jaundice. The rise in phosphatase in the former type was attributed to the re-absorption into the blood-stream of

bile which has a high phosphatase content. Bodansky and Jaffe (15) also came to the conclusion that the liver was an important source of plasma phosphatase and that where excretion of bile is diminished but production of the enzyme by the liver cells is not affected, the amount of plasma phosphatase increases. Ligation of the bile ducts in dogs has been found to produce a very great increase in plasma phosphatase which returns to normal levels after the obstruction has been removed. Bodansky and Jaffe (18) found that in these cases of experimental biliary obstruction the rise in phosphatase did not run parallel with that of plasma bilirubin. Austoni and Coggi (8) by *in vitro* experiments demonstrated that while bilirubin did not appear to affect phosphatase activity the addition of sodium glycocholate or taurocholate had a definite inhibitory effect. Hartman and Schelling (40) produced functional hepatic inefficiency by means of Eck fistula, X-ray irradiation, and CCl_4 and found that the increase in phosphatase ran parallel with changes in cholesterol partition, increase in serum bilirubin, and retention of bromsulphalein. Recently, however, Armstrong and Banting (6) have stated that the plasma phosphatase may actually be increased after hepatectomy; they believe that the bones constitute the sole source of serum phosphatase. From the diagnostic point of view doubt has been thrown upon the value of plasma phosphatase estimations. Greene et alii (34) found that the figures for plasma phosphatase in obstructive jaundice (18 cases) varied from 11.6 to 63.2, in hepatitis (12 cases) from 8.4 to 72.2 and in portal cirrhosis from 1.3 to 19.9. Fiesinger and Boyer (31) also found that increase in plasma phosphatase was not limited to cases of obstructive jaundice but was met with in hepatitis. Cantarow (22) has reported similar findings. In our own series of 25 patients with jaundice the plasma phosphatase was increased when the cause was obstruction or some form of hepatitis, but there was overlapping in the values obtained for these two groups. In the 15 patients with haemolytic jaundice normal values were obtained except in the three with icterus gravis: in these the plasma phosphatase was definitely increased. From an investigation of 70 cases with various types of jaundice, Herbert (41) concluded that the diagnostic value of the estimation of plasma phosphatase was limited by the fact that moderate rises may occur both in obstructive and in toxic-infective jaundice. She is of the opinion that in the latter condition there may be some biliary obstruction together with increased formation of bilirubin in the body and that the small rise in plasma phosphatase can be attributed to the incompleteness or short duration of the biliary obstruction. Certainly her figures show that the highest phosphatase values were obtained most frequently in cases where the obstruction was continuous and prolonged as in malignant disease, rather than in those where it was intermittent or recent. The figures for phosphatase and directly reacting bilirubin in the plasma did not run parallel, but this might be due to the fact that damaged liver cells may allow a diffusion of bilirubin but not of phosphatase from the bile canaliculi into the blood-stream.

Anderson (5) from an examination of 23 cases observed that the phosphatase was high in obstructive jaundice and normal or only moderately raised in toxic and infective jaundice, but found there was too much overlapping of the figures for a phosphatase estimation to be a reliable test in the differential diagnosis of the two types of jaundice. In order to explain the absence of correlation between phosphatase and bilirubin he suggested that whereas an increase of bilirubin in the plasma may result from increased production of this pigment, damage to liver cells or obstruction to bile canaliculi, an increase in phosphatase results only when the bile passages are obstructed.

Fiessinger and Boyer (31) observed that in eight cases with marked hepatic insufficiency only two showed any increase in plasma phosphatase, and that only slightly. They concluded that any rise in plasma phosphatase observed in jaundice could not be attributed to defective liver function. In view of the fact that leucocytes are rich in phosphatase they considered the possibility of these cells being the source of the increased plasma content. Although they found that it was very difficult to liberate the phosphatase from the white cells into the plasma *in vitro* they think that it is just possible that leucocyte phosphatase may pass into the plasma *in vivo* in cases of jaundice.

Austoni and Coggi (8) are of the opinion that the rise in plasma phosphatase in cases of obstructive jaundice is due not to the retention of phosphatase which is normally excreted in the bile but to the disturbance in calcium and phosphorus metabolism which takes place when bile is absent from the duodenum. Indeed, in one case they found that removal of the bile by an external biliary fistula resulted in a marked increase in plasma phosphatase. It is well-known that a defective flow of bile into the small intestine is accompanied by a great decrease in the retention of lime as a result of defective absorption. Indeed, prolonged removal of bile by a gall-bladder fistula results in extensive osteoporosis. In haemolytic jaundice bile enters the intestine and the absorption of minerals is not significantly disturbed. Austoni and Coggi (8) report one case which is of great interest in this connexion: an external choledochostomy was produced in a case of jaundice and, despite the fact that bile was being drained away, the plasma phosphatase steadily increased.

Recently in collaboration with Mr. A. B. Kerr we have been able to estimate the plasma phosphatase at weekly intervals in a patient with an external biliary fistula. During the period when no bile was entering the gut, the plasma phosphatase increased steadily to about four times the normal value although there was no jaundice. Within ten days of bile appearing in the motions the plasma phosphatase began to diminish. In this case, therefore, the increase in plasma phosphatase took place when calcium absorption was in all probability defective, thus supporting the view that even in jaundice the height of the plasma phosphatase depends on the extent to which the calcium requirements of the bones are satisfied.

Miscellaneous

In no other clinical condition has a marked deviation of the plasma phosphatase value from normal been reported. The findings in various pathological states will therefore be but briefly recorded.

Disorders of growth. In both cretinism and achondroplasia Smith (77) obtained low values for plasma phosphatase. Duvoir et alii (29) record a low figure in an infant with achondroplasia, but Bodansky and Jaffe (16) obtained normal values in three patients, and our own figures for three cases are low but within normal limits. Bodansky and Jaffe (16) found in one case of cretinism that the plasma phosphatase increased after thyroid treatment, but we failed to observe any change over a period of four weeks in two infants with cretinism who had received thyroid treatment. In renal and coeliac dwarfism we have found that the plasma phosphatase tends to be on the low side unless a rachitic process is present when a high value is obtained. In both acromegaly and hyperthyroidism slight increases have been reported (16) (48).

Ectopic calcification. In calcinosis, plasma phosphatase did not vary from normal (16). Wilkins, Regen, and Carpenter (84) recorded high values for phosphatase activity in samples of muscle and fibrous tissue obtained in the pre-ossification stage from a patient with myositis ossificans, and Simmons and Franseen (76) found a considerable increase in plasma phosphatase in a patient one month after the injury when there was great osteoblastic activity in the lesion, but only a slight increase later when the heterotropic bone was of a more adult character. Pautrat (66) obtained slightly increased values in patients with phosphatic calculi but no departure from normal when the stones were uratic in nature. In seven children with bladder or kidney stones all composed of phosphates, we found no increase in plasma phosphatase.

In the acute stage of scurvy, whether or not sub-periosteal haemorrhages were present, the plasma phosphatase had a low normal value which rose with the onset of calcification of the haemorrhages and fell again as absorption took place (78).

Renal disease. In spite of the fact that renal cells are known to produce phosphatase and that the phosphatase activity of renal tissue is reduced in chronic nephritis (21), significant changes in plasma phosphatase have been recorded in patients with renal disease (48). In 47 children with varying forms of acute nephritis we found that only three had values for plasma phosphatase which exceeded normal limits, and then but slightly.

Diabetes mellitus. In this condition Kay (48) obtained values which were slightly above normal. Pautrat (66) in 15 out of 20 cases found a high plasma phosphatase, the increase being greatest in the patients with uncomplicated diabetes. We obtained data in 17 diabetic children in all but one of whom the phosphatase was definitely increased. Injection of insulin produced no immediate effect on the phosphatase level nor could any relationship be detected between the phosphatase value and the height of the

blood-sugar, blood cholesterol, or blood fat or the general clinical condition. This is in accord with the experimental results of Binet and Pautrat (11) who found that removal of the pancreas from dogs led to an increase in plasma phosphatase which still persisted even after the hyperglycaemia was controlled by insulin. Kay (48) recorded a high value in a patient with

TABLE I

Normal Values for Plasma Phosphatase According to the Various Methods of Estimation.

Method.	Adults.		Children.	
	Max. units.	Min. units.	Max. units.	Min. units.
Bodansky (16) (17)	4.0	1.5	12.0	5.0
Cayla (24) (27)	15.0	10.0	40.0	35.0
Jenner-Kay (46) (59)	7.9	3.2	11.0	3.4
Kay (48)	0.21	0.10	0.34	0.17
King-Armstrong (51) (19)	13.1	3.7	20.0	15.0
Roberts (70)	5.5	3.0	—	—

TABLE II

Serum Calcium and Inorganic Phosphorus and Plasma Phosphatase in Various Affections of the Bones.

Disease.	Serum calcium.	Serum phosphorus.	Plasma phosphatase.
Osteitis deformans (Paget's)	N	N	+++
Generalized osteitis fibro-cystica (Recklinghausen's)	++	—	+++
Solitary bone cysts (single or multiple)	N	N	N or +
Myeloma	N or +	N or +	N
Metastatic bone cancer	+	+	++
Osteogenic sarcoma	+	+	++
Other bone tumours	N	N	N
Rickets	N or —	—	++
Osteomalacia	N or —	—	++
Osteogenesis imperfecta	N	N	N or +
Senile osteoporosis	N or —	N	N

hypercholesterolaemia associated with xanthomatosis. In one patient with xanthomatous deposits in the bones and a high blood cholesterol we found that the plasma phosphatase fell within normal limits. Furthermore in nephritic patients with hypercholesterolaemia, normal values were obtained so that a high blood cholesterol *per se* is not responsible for an increase in plasma phosphatase.

Blood diseases. Umeno (82) found increased values in patients with leukaemia, but Iwatsuru and Minamy (45) state that the increase only occurs when the leukaemia is of the myeloid type. In erythroblastic anaemia and Hodgkin's disease normal values have been recorded (86). In Gaucher's disease there is an increase which appears to be related to the degree of bone resorption (16).

Non-osseous tuberculosis. Mussa (61) found that in seven out of ten children with non-osseous tuberculosis the plasma phosphatase was reduced. Binet and Pautrat (10) obtained low values in 12 patients with febrile generalized tuberculosis but normal results in 13 tubercular patients whose general condition was good. In five patients we found values ranging from a very low level to one slightly above normal.

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THE LIOPENIA OF HYPERTHYROIDISM¹

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STUDIES on the effect of thyroid disease upon the concentration of lipids in blood other than cholesterol have been few in number. The majority of investigators agree that blood cholesterol is decreased in hyperthyroidism. This was demonstrated in 1922 by Epstein and Lande (21), and has been also found by Bing and Heckscher (5), Mason, Hunt and Hurxthal (35), Hurxthal (27), and Lahey (29). Others have not been able to obtain as consistent results, for example, Parhon and Parhon (41), Wade (46), Bonilla and Moya (7), and Grabfield and Campbell (22). There are several possible explanations for this apparent discrepancy. In the first place, the reciprocal relation between blood cholesterol and the basal metabolic rate is shown in the composite curve presented by Cutting, Rytand and Tainter (19) to be less obvious in cases of hyperthyroidism than in hypothyroidism. A second factor of probable importance is that many of these studies were performed on whole blood; as found by Boyd (11), changes in the concentration of blood lipids usually take place in plasma and not in the red-blood cells, the net result being less obvious changes in whole blood. Boyd and Connell (17) have shown that this is likewise true in disease of the thyroid gland. Apart from these studies on blood cholesterol, the total fatty acid content of the plasma was noted to be low in hyperthyroidism by Nicholls and Perlzweig (37).

A number of related experiments have been performed on other species. In *dogs*, hyperthyroidism has been found associated with a decrease in blood cholesterol by Blinoff (6), Parhon and Derevici (39), and Pugsley (43). In *cats*, thyrotropic hormone prevents the development of a post-prandial lipemia according to Silberstein, Gottdenker and Geiger (45), suggesting that the relation of blood lipids to hyperthyroidism in cats is similar to that in dogs. On the other hand, hyperthyroidism in *rabbits* may apparently be associated with decreased amounts of blood lipids (28, 47), increased amounts (44), or with variable effects (42). The cholesterol content of the blood of *birds* was noted to be raised in hyperthyroidism by Parhon and Parhon (41).

Hyperthyroidism in man, induced by the administration of various thyroid preparations, has in general been found associated with decreased amounts of blood cholesterol and of one or two other lipids. In 1918, Luden (33) found that thyroid feeding lowered the percentage of blood cholesterol in

¹ Received February 16, 1937.

patients with malignant disease. This effect of thyroid feeding has been confirmed in other types of patients, chiefly those with disease of the thyroid gland, by Leupold (31), Lévy (32), Parhon and Ornstein (40), Duncan (20), Hess (25), Zolotareva et al. (48), Hepler (24), and Boyd and Connell (17). In 1925, Bing and Heckscher (5) recorded that thyroïdin did not lower the percentage of blood lipids in patients with nephritis, and in 1936 Page and Farr (38) demonstrated the same for patients with nephrosis.

From these several studies one may conclude that hyperthyroidism in man is accompanied by a decrease in the concentration of blood cholesterol, and *probably* of other lipids, the decrease being less marked and frequently insignificant if whole blood rather than plasma be analysed. The administration of thyroid to man lowers the percentage of blood cholesterol, and *probably* of other lipids in patients with disturbances of the thyroid gland and certain other diseases, with the conspicuous exception of some types of nephritis. The lipopenic action of the thyroid hormone is not common to all species of animals, being seen in cats and dogs, but not in rabbits and birds.

The present communication is concerned with more complete data showing the effect of increased activity of the thyroid gland upon the concentration of all known lipids in the blood of man. Inasmuch as there was found to be a significant decrease in the percentage of plasma lipids, the condition has been called the lipopenia of hyperthyroidism. The term lipopenia was introduced by Boyd (12) to indicate the occurrence of a decrease in the amount of lipids in blood.

Forty-three patients were studied from the medical and surgical services of the Kingston General Hospital. In this report are included only those cases in which there was an indisputable diagnosis of hyperthyroidism which was later found to respond to the usual treatments. Oxalated blood was used and extracts of plasma and of the red-blood cells were prepared immediately after taking the specimen from the patient. Boyd and Murray (18) have shown that the lipid content of oxalated plasma begins to increase about eight hours after removal from the patient. The method of cold extraction was used (14, 15) and the filtered extracts analysed by Bloor oxidative micro-methods as modified by Boyd (9, 10, 13). The lipid content of the red-blood cells was not found significantly different from normal in conformity with the studies of Boyd and Connell (17), and of Boyd (16), and hence only values for plasma will be reported.

Results

The values found for the 43 cases of hyperthyroidism have been presented in Table I. A statistical analysis of these figures has been made using formulae previously given (11). Such data have been compared with corresponding values for normal human adults obtained by the same methods and already described (11).

The lipid composition of plasma in hyperthyroidism. The total lipid content

of plasma was found to extend from 268 to 551 mg. per cent. (milligrammes of total lipid per 100 cubic centimetres of plasma) with a mean of 428 mg. per cent. and a standard deviation of 63 mg. On the average the total lipid was composed of the following fractions: 32 per cent. of cholesterol esters, 29.5 per cent. of neutral fat, 29 per cent. of phospholipid, and 9.5 per cent. of free cholesterol. In contrast the total lipid of plasma in normal human adults consists on the average of 34.5 per cent. of cholesterol esters, 32 per cent. of phospholipid, 25 per cent. of neutral fat, and 8.5 per cent. of free cholesterol. At first sight it might appear that there is no significant difference in these values. They would indicate that in hyperthyroidism there is relatively slightly more neutral fat and free cholesterol, and relatively slightly less phospholipid and cholesterol ester, than in the composition of plasma total lipid for normal adults. By themselves these comparisons would mean nothing since the differences were very slight. They will, however, be shown to be significant from a statistical analysis of the results to be later described.

The *total fatty acid* content varied between 177 and 367 mg. per cent. with a mean of 258 mg. per cent. and a standard deviation of 51 mg. The fractions composing the total fatty acid have not been indicated in Table I, but may be calculated from the data given by means of factors previously discussed (10). On the average, there were 120 mg. of neutral fat fatty acids or 46.5 per cent. of the total fatty acid, 84 mg. of phospholipid fatty acids or 32.5 per cent. of the total fatty acid, and 54 mg. of cholesterol ester fatty acids or 21 per cent. of the total fatty acid. The total fatty acid of plasma in normal human adults is composed on the average of 40 per cent. of neutral fat fatty acids, 37 per cent. of phospholipid fatty acids, and 23 per cent. of cholesterol ester fatty acids. These figures indicate that there are relatively smaller average amounts of phospholipid fatty acids and cholesterol ester fatty acids, and relatively more neutral fat fatty acids in the total fatty acid of plasma in hyperthyroidism than in normal human adults. Such conclusions are in conformity with those previously discussed under the composition of total lipid.

The *total cholesterol* values extended from 69 to 163 mg. per cent. with a mean of 122 mg. per cent. and a standard deviation of 20 mg. The 122 mg. of total cholesterol were made up of an average of 81 mg. of ester cholesterol or 66 per cent. of the total cholesterol and 41 mg. of free cholesterol or 34 per cent. of the total cholesterol. Ester cholesterol ranged in value from 39 to 113 mg. per cent. and the standard deviation of the mean was 18 mg. The concentration of free cholesterol extended from 25 to 58 mg. per cent., and the standard deviation of the mean was 8 mg. The total cholesterol of plasma in normal human adults is composed, on the average, of 71 per cent. of ester cholesterol and 29 per cent. of free cholesterol. Thus it is apparent that ester cholesterol made up relatively less, and free cholesterol relatively more, of the total cholesterol of plasma in hyperthyroidism than in normal human adults.

TABLE I

The Lipid Composition of Blood-plasma in Hyperthyroidism. The Results are expressed in mg. per 100 c.c. of Blood-plasma.

Number.	Total lipid.	Composition of total lipid.					
		Neu- tral fat.	Total fatty acids.	Cholesterol.			Phos- pho- lipid.
				Total.	Ester.	Free.	
Hyperthyroidism.							
1	268	129	178	69	39	30	44
2	324	47	180	93	53	40	148
3	331	46	177	109	72	37	128
4	339	51	182	111	72	39	129
5	341	114	207	98	57	41	91
6	353	137	233	76	44	32	111
7	355	119	218	103	72	31	85
8	360	0	181	115	80	35	191
9	367	127	233	89	51	38	117
10	367	120	222	111	79	32	83
11	368	46	199	118	84	34	148
12	372	82	215	108	70	38	135
13	395	138	236	125	78	47	80
14	415	100	245	136	111	25	88
15	418	179	274	110	81	29	75
16	418	43	207	163	109	54	139
17	418	93	229	151	113	38	98
18	420	105	241	134	89	45	121
19	420	56	215	136	90	46	168
20	422	125	267	95	59	36	162
21	424	76	235	134	93	41	152
22	430	125	250	141	99	42	98
23	433	83	250	124	93	31	164
24	433	126	263	117	75	42	140
25	443	175	280	128	91	37	79
26	447	123	254	153	101	52	103
27	447	86	249	144	98	46	151
28	450	100	252	149	102	47	133
29	460	92	260	141	97	44	162
30	460	150	288	113	67	46	152
31	466	76	264	135	99	36	188
32	471	237	318	112	54	58	86
33	481	179	315	107	67	40	150
34	481	188	307	130	88	42	104
35	493	152	299	141	96	45	136
36	499	231	330	127	77	50	89
37	507	193	326	128	83	45	130
38	511	146	315	124	70	54	195
39	513	183	321	140	90	50	130
40	518	220	347	114	69	45	138
41	520	154	313	147	94	53	156
42	521	245	345	138	90	48	78
43	551	237	367	127	77	50	135
Mean	428	126	258	122	81	41	125
Standard deviation	63	59	51	20	18	8	35
Standard deviation in per cent. of mean	15	47	20	16	22	19	28
Expected range of 2/3 of cases	365-491	67-185	207-309	102-42	63-99	33-49	90-160
Expected range of 95 per cent. of cases	302-554	8-244	156-360	82-162	44-117	25-57	55-195
Average percentage decrease from nor- mal	31	18	30	33	37	23	36

TABLE I (continued)

Number.	Total lipid.	Composition of total lipid.					
		Neu- tral fat.	Total fatty acids.	Cholesterol.			Phos- pho- lipid.
				Total.	Ester.	Free.	
		Normal adults.					
Mean	617	154	362	181	128	53	195
Standard deviation	75	77	62	22	23	10	37
Expected range of 2/3 of normal cases	542-692	77-231	300-424	159-203	105-51	43-63	158-232
Expected range of 95 per cent. of normal cases	467-767	0-308	238-486	137-225	82-174	33-73	121-269

The two remaining lipids to be considered are *neutral fat* and *phospholipid*. Values for neutral fat were found between 0 and 245 mg. per cent. with a mean of 126 mg. per cent. and a standard deviation of 59 mg. The percentage of phospholipid extended from 44 to 195 mg. per cent. with a mean of 125 mg. per cent. and a standard deviation of 35 mg.

The mean lipopenic changes in hyperthyroidism. For purposes of comparison, mean values of lipids in the plasma of normal human adults, previously found by these same methods (11), have been included in Table I. The mean values in hyperthyroidism subtracted from the mean values of normal adults, and expressed as a percentage of the latter means, have also been listed in Table I. On the average, the total lipid of plasma was 69 per cent. of that in normal adults, there being a decrease of 31 per cent. in the lipid content of plasma in hyperthyroidism.

The individual lipids were not decreased in value all to the same extent. The greatest loss occurred in the cholesterol ester fraction, and in the phospholipids, in which the mean losses were 37 and 36 per cent. respectively. The decrease in free cholesterol was less marked, averaging 23 per cent., and the least decrease occurred in the neutral fat fraction, averaging 18 per cent. These changes are in general agreement with those previously recorded by Boyd (12) as characteristic of the lipopenia of fever. The similarities between the lipopenias of fever and of hyperthyroidism, and of certain other conditions now under investigation, would suggest that a variety of stimuli may produce the same result, probably by acting through a single mechanism or organ controlling that mechanism. There is a good deal of evidence which cannot be reviewed here and which, with data obtained by one of us but unpublished (E. M. B.), would indicate that the liver is the organ responsible for the development of a lipopenia. Briefly it would appear that neutral fat is brought to the liver from the fatty storage tissues and from the gut, and in the liver is converted into phospholipid and cholesterol esters, these then entering the blood-stream. Under the influence of certain stimuli such as toxic substances or endocrine products, it would seem that the liver loses part of its capacity to function thus. As a result there occurs a decrease in the concentration of phospholipid

and of cholesterol esters in plasma. It would seem most likely that the decrease in plasma phospholipid, which tends to hold other lipids in 'solution', prevents plasma from taking up the usual amounts of neutral fat and of cholesterol, both of which are relatively more 'insoluble'. There is at present no satisfactory explanation as to the site of origin of the plasma lipids, and the above mechanism is at present used as a working hypothesis by one of us (E. M. B.); and, taken provisionally as it is intended to be, has served to link together many otherwise isolated facts.

The statistical significance of the lipopenia of hyperthyroidism. The statistical significance of the variations found in the lipid content of blood-plasma in hyperthyroidism may be judged by considering the means and standard deviations of the means with the corresponding values in normal human adults as listed at the bottom of Table I.

The expected range of total lipid of plasma, in two-thirds of cases with hyperthyroidism, was calculated to lie between 365 and 491 mg. per cent., and this range may be seen not to overlap the corresponding range for normal adults which was from 542 to 692 mg. per cent. On the other hand, some overlapping occurred with the ranges which included 95 per cent. of cases in both groups. It is therefore apparent that more than five out of six cases with hyperthyroidism may be expected to have values for total lipid of plasma below more than five out of six normal adults. There is thus a significant decrease in the lipid content of plasma in hyperthyroidism.

In a similar manner it may be shown that approximately five out of six, and occasionally more of the expected values in hyperthyroidism lie below approximately five out of six, and occasionally more of the expected values in normal adults for total fatty acid, total cholesterol, ester cholesterol, free cholesterol, and phospholipid. The concentration of all these lipids is thus significantly lowered in hyperthyroidism. Neutral fat was the only lipid in which a significant difference could not be shown to exist. In other words, values for plasma neutral fat in hyperthyroidism may lie—and many do, as seen in Table I—within the normal range.

The relative variation of plasma lipids in hyperthyroidism. The relative variations of values may be estimated by computing the standard deviation as a percentage of the mean. Such values, known as the percentage standard deviations, have been listed in Table I. The least variation occurred with total lipid and total cholesterol, the standard deviations being 15 and 16 per cent. of the respective means. Variations in values for free cholesterol, total fatty acids, and ester cholesterol were slightly greater, the standard deviations being 19, 20, and 22 per cent. of the respective means. The variation of values for phospholipid were still greater, the percentage standard deviation being 28 per cent. The greatest variation occurred in the neutral fat values, the standard deviation being almost one-half of the mean. It may be shown that the relative variation of values for plasma lipids in hyperthyroidism was about the same as that

in normal adults, thus showing that the statistical significance deduced above was not due to the chance selection of cases with a comparatively narrow range of values.

Discussion

It has been shown that in hyperthyroidism there occurs a lipopenia due to a significant decrease in the concentration of lipids in blood-plasma. The percentages of all lipids were found to lie significantly below normal, except that of neutral fat, which was found within the normal limits. An explanation of these changes, as due to the effect of the thyroid hormone upon the function of the liver in synthesizing cholesterol esters and phospholipids, has been provisionally offered.

A number of other explanations have been proposed purporting to explain the effect of the thyroid gland upon the concentration of blood lipids, more especially blood cholesterol which has been studied more extensively than other lipids. Blood cholesterol has been frequently found to vary inversely with the basal metabolic rate in disease of the thyroid gland. It does not appear, however, that the changes in the basal metabolic rate *per se* are of significance as an explanation. In conditions other than thyroid disease we have not, in this clinic, found any consistent relation whatsoever between basal metabolism values and the concentration of blood lipids. In 1918 Luden (33) found that radium decreased the basal metabolic rate in malignancy, and a decrease also occurred in blood cholesterol at the same time. Cutting, Rytand, and Tainter (19), and Grant and Schube (23) found that dinitrophenol increased the basal metabolic rate and also blood cholesterol. In the experiments of Grant and Schube (23) the blood cholesterol subsequently fell in value, but later rose again and bore no relation to changes in the basal metabolic rate.

The lipaemia produced in dogs by administration of olive oil is decreased by the administration of the thyrotropic hormone of the anterior pituitary gland (45) and by thyroid itself (30). Fat tolerance tests in man, as related to thyroid feeding have produced rather variable results (24). Although thyroid feeding, appears to diminish the extent of a post-prandial lipaemia, this information cannot be taken as evidence that the thyroid hormone increases the rate of uptake of lipids from blood by the tissues. It might also be due to decreased absorption of fat or to failure of ingested fat to be 'dissolved' to any great extent by a plasma already deficient in phospholipid.

Loss of weight is a major symptom of hyperthyroidism and may be taken as evidence of a relative malnutrition. Man and Gildea (34) have recently presented data from which they conclude that malnutrition may itself lower the concentration of blood lipids. It may be noted that most of their cases had a fever and/or anaemia; and which of the many factors was, or were responsible for the decrease in the percentage of blood lipids in their

cases is difficult to decide. Borruso (8) was unable to find any significant alteration in blood-fat in emaciation occurring in old age.

There has been much work done upon the effect of thyroid substance on the activity of lipolytic enzymes in serum and tissues, and it is probable that some of these studies have a bearing on the cause of the lipopenia of hyperthyroidism. Thyroid extracts have been found to diminish or inhibit the lipase of blood-serum of man by Achard and Clerc (1), of rabbits by Bach, Lovas and Neufeld (2), and of cats by Bauer and Hoffmann (4). According to Bauer and Feil (3), who found that thyroxine diminished the lipase content of the liver in mice, the fall in serum lipase is due to decreased production of lipase by the liver. It is by no means certain, however, that serum lipase originates in the liver; Hiruma (26) found that blood of the pancreatico-duodenal vein contained more lipase than portal vein blood and suggested that lipase was produced in the pancreas and carried to the liver. A number of investigators have studied the effect of thyroid substances upon the lipid composition of the liver, but there has arisen as yet no uniformity of results from such work, probably because such factors as dosage, species, diet, &c., have not been sufficiently taken into consideration. Hepatic tissue is not the only tissue whose lipolytic activity is impaired by the thyroid; Mühlbock and Kaufmann (36) found a decrease in the lipase of adipose tissue. There remains a good deal to be desired in these studies of lipolytic enzymes.

Summary

The lipid composition of blood plasma of 43 cases of hyperthyroidism in man was determined by oxidative micromethods. There was found present a lipopenia with the following mean values and standard deviations of the means:

Total lipid	428 ± 63 mg. per cent.
Neutral fat	126 ± 59 " "
Total fatty acid	258 ± 51 " "
Total cholesterol	122 ± 20 " "
Ester cholesterol	81 ± 18 " "
Free cholesterol	41 ± 8 " "
Phospholipid	125 ± 35 " "

Compared with corresponding values for normal human adults, these results indicated that there was a significant decrease in the concentration of all lipids in blood plasma, except neutral fat, which was usually found within the normal range.

This work was aided financially by the Alice F. Richardson Fund of the Kingston General Hospital.

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THE INFLUENCE OF THE CEREBROSPINAL FLUID IN ACROMEGALY ON THE URINARY EXCRETION OF CHLORIDES¹

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With Plate 7

In November 1935 the patient M. R., a spinster aged 32, was sent to consult Mr. Cecil Joll, at the Royal Free Hospital, with reference to an enlargement of the thyroid gland, first noted a year previously. In view of acromegalic and virile traits, she was transferred to the medical side, under the care of one of us (D. C. H.).

The first indication of any departure from normal was in 1926, when the hands and feet began to enlarge, and the patient gained weight, some three stone in the next five years. The size in gloves changed from 6 $\frac{3}{4}$ to 7 $\frac{1}{2}$, and extra large boots were made to order. In about 1930, some four years after the appearance of acromegalic traits, virilism developed. Coarse hair grew on the face, especially the beard region, and on the trunk, arms, and thighs. The hair on the head became thick and coarse, but there was some retraction in the fronto-parietal region. The voice became hoarse and deep, and the patient's sister complained that she spoke like a man. The breasts became notably smaller, but menstruation occurred regularly at intervals of one month, and lasted some five to seven days. Generalized headaches had been troublesome for the past few months. The patient's previous history and her family history were uneventful.

On first examination (cf. Plate) the facies was typically acromegalic, with marked prognathism, the lower teeth being widely spaced, and nose and lips enlarged. The skin was thick, coarse, and greasy, with wide pores, and some acne. The hands and feet were considerably enlarged, and the fingers broad and stumped. Her face, trunk, and limbs were covered with coarse hair, distributed in the male pattern, as is seen with adrenal tumours. There was a moderate excess of fat over the chest, neck, shoulders, and abdomen. The weight was 10 stone 12 lb. and the height 5 feet 2 inches. The breasts were small, but the uterus and external genitals not abnormal (Professor Fleming). The blood-pressure was 120/80 mm. Hg. There was a diffuse enlargement of the thyroid gland, right side more than left, but apart from a somewhat rapid pulse of 100, there were no gross signs of thyrotoxicosis. The fundi and fields of vision were normal (Miss Mann). There was some lymphatic hyperplasia in the tonsillar and adenoid region. The cardiac, pulmonary, and neurological systems were apparently normal.

The fasting blood-sugar was normal, 90 mg. per cent., and a carbohydrate tolerance test, with 100 grm. glucose, on 29th November, 1935, gave the following values at half-hour intervals: 90, 150, 160, 140, 155, 110 mg. per

¹ Received February 1, 1937.

cent.; on the 7th February, 1936, a similar test gave the following blood-sugar values: 90, 150, 220, 210, 162 mg. per cent.; on 24th February, 1936, 108, 182, 195, 168, 160, 106 mg. per cent. All three curves showed a delayed fall in blood-sugar, and in the latter two, the intermediate values were above normal.

The basal metabolic rate was +5 per cent. A test meal, with and with-

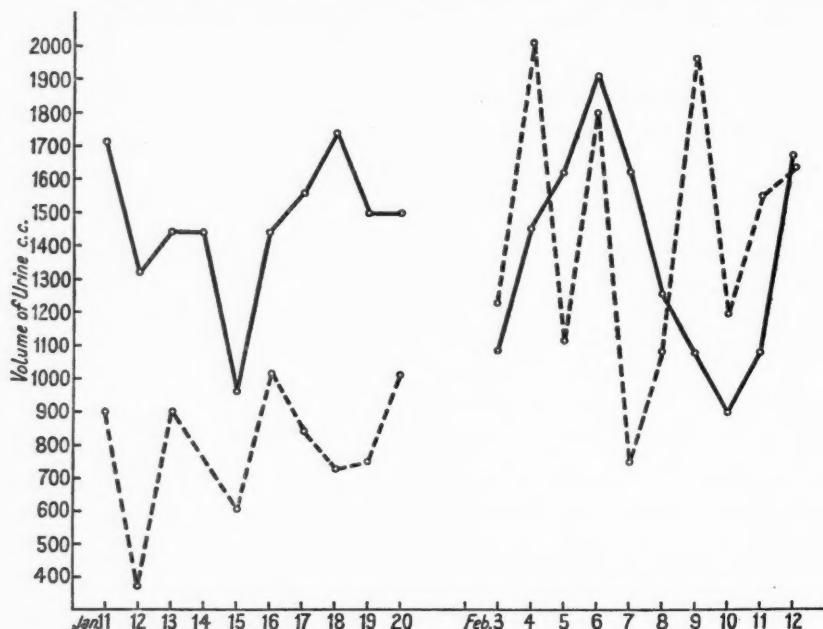


FIG. 1. To show relatively small daily volume of urine of the acromegalic, compared with fluid intake, and the effect of pituitary radiation in producing a balance between fluid intake and output.

— volume of fluid taken c.c.
 - - - - - volume of urine excreted c.c.

out histamine, gave normal values. The plasma chloride content was normal, 572 mg. per cent., as was also the sodium, 325 mg. per cent. The blood urea was 30 mg. per cent. A blood count was as follows: Hb. 104 per cent., erythrocytes 5,470,000, colour index 0.94, leucocytes 10,400, polymorphonuclear cells 74 per cent., lymphocytes 20 per cent., eosinophils 1.5 per cent., mononuclears 4.5 per cent. The urine contained no sugar or albumin.

Radiography showed considerable enlargement of the pituitary fossa, the anterior-posterior diameter measuring 22 mm., and much thickening of the skull. There was no osteoporosis of any of the bones. The blood calcium was within normal, 11.0 mg. per cent., the phosphorus 2.6 mg. per cent., and the phosphatase 0.15 units. Uroselectan and retrograde pyelography gave no indication of an adrenal tumour. Electrocardiographic examination: regular rhythm, no preponderance, T_1 large, T_2 small, T_3 inverted.

Deep radiation, directed to the pituitary gland, was carried out by Dr. Ulysses Williams during the latter half of January and first half of February 1936. The most striking result was the diminution in the amount

of perspiration and the increase in the volume of urine excreted (Fig. 1), so that fluid intake and output became balanced. The hair on the face and trunk appeared to grow less readily and was less coarse in texture. The patient was of the opinion that her lower jaw was less awkward in movement. The facial appearance was not so plethoric, and the number of erythrocytes fell from 5,470,000 to 4,590,000. The basal metabolic rate was practically unchanged, plus 5 per cent. before radiation, minus 1.5 per cent. after. The carbohydrate tolerance was not improved.

The presence of virilism, and the knowledge that hyperplasia of the adrenal cortex, with or without adenomata, is a not infrequent pathological finding in acromegaly, suggested the possibility of the secretion by the patient's pituitary gland of the adrenotropic hormone. Some preliminary experiments on hypophysectomized rats were kindly undertaken by Dr. M. Klein (working in Dr. A. S. Parkes's department at the National Institute of Medical Research), and positive evidence of adrenotropic activity of the patient's serum was obtained. The evaluation of the specificity of this reaction and its quantitative significance, compared with adequate controls, await further investigation.

Evidence of Secretion of the Antidiuretic Hormone into the Cerebrospinal Fluid

According to Atkinson (1), polyuria occurs in 44.5 per cent. of acromegalics, and may be a true diabetes insipidus, but the opposite condition, observed clinically in this patient, is, as far as can be gathered from the literature, a rarity. It is not difficult to conceive of an enlargement of the anterior lobe of the pituitary gland affecting the posterior lobe and (or) its neural connexions, either in the direction of destruction or of irritation.

In January, 1936, it was observed that the daily urinary output of the patient, M. R., was subnormal, e.g. 600 c.c., and further observation (Fig. 1) showed that there was a constant excess of fluid intake over output. There was, nevertheless, no gain (or loss) in weight, and during the same period the patient perspired very freely, drops of perspiration rolling down her back and chest. Some degree of excessive perspiration had been present for four years.

Experiments were therefore devised to ascertain if an excess of anti-diuretic hormone was being secreted by the pituitary gland. Although both serum and cerebrospinal fluid were examined, the latter might be regarded as more likely to yield positive results, since (a) it contains less solids and less protein (than the serum) which might interfere with the action of the antidiuretic hormone, and (b) on general grounds, the hormone would probably be found in greater concentration in the spinal fluid. Both serum and spinal fluid from the patient, and from normal controls, were subcutaneously injected into rabbits, after the oral administration of 150 c.c. of water, and the effect on urinary and chloride excretion observed (Figs. 2, 3, 4, and 5).

On 22nd January, 4th February, and 12th March, lumbar punctures were performed between the third and fourth lumbar vertebrae. On each

occasion, but especially on the first and second, the spinal fluid appeared to be under considerable pressure. The fluid was collected into glass test-tubes and immediately transferred to the Lister Institute for the rabbit experiments. Control specimens of spinal fluid were obtained from three organically normal patients of approximately the same sex and age, and we are greatly indebted to Dr. J. B. Pennybacker for these specimens.

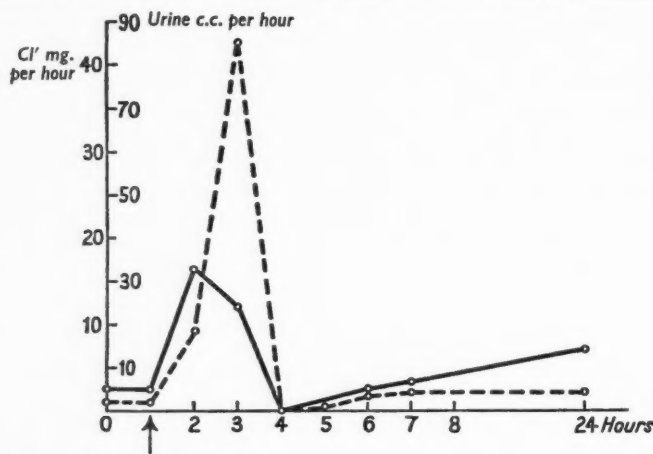


FIG. 2. To show the effect of 150 c.c. of water per os, given at arrow, on urinary and chloride excretion of a rabbit. Experiment I.

Ordinates—chloride excretion, Cl' mg. per hour, e.g. 10; urinary excretion c.c. per hour, e.g. 10.

Abscissae—hours.

————— chloride. - - - - - urine.

Technique of the rabbit experiments. The effect of the injections of spinal fluid (acromegalic and controls) on the water diuresis of rabbits was examined by a method similar to that used by Janssen (3), and that on the chloride excretion was estimated by Volhard's method; the total solids present in the urine were also recorded. As often repeated catheterization, even most carefully carried out, leads to injury and infection of the mucous membrane, preliminary experiments were carried out to evacuate the bladder by pressure, in a manner that would yield accurate quantitative results. From a large number of female rabbits (average weight 2 to 3 kg.), only those found to be suitable for the purpose were selected for further experiments. For some days they were fed with as much cabbage as they wanted, and their body-weight and spontaneous daily output of urine recorded. When an equilibrium was attained, the cabbage was replaced by oats on the evening before the day of the experiment. The next morning the rabbits were given 150 c.c. of tap-water through a stomach tube. Immediately before, and at hourly intervals after the administration of the water, the urine was pressed out of the bladder; the volume, specific gravity, and chloride content were estimated. The animals were kept in metabolism

cages, and the urine spontaneously passed in the period of observation was added to that expressed manually during the same period. Both at the beginning and the end of each experiment the animals were weighed to see if water had been retained. Such preliminary water experiments were repeated several times at intervals of a few days. For the final experiments with the spinal fluids, only those animals were selected which eliminated, within five hours, the water administered, and whose weight gave no indication of water retention. With any one animal, following the administration of 150 c.c. tap-water, the curve of urine elimination and chloride excretion tended to be similar in repeated experiments (Fig. 2). In the subsequent experiments with rabbits that behaved fairly consistently, the spinal fluids of the acromegalic patient and of control normal patients were injected subcutaneously, at the same time as the water was administered by stomach tube (Figs. 3, 4). For comparison, a standardized solution of pitressin (Parke, Davis & Co.) was injected in other experiments (Fig. 5). The first specimen of spinal fluid was obtained before a sufficient number of standardized rabbits were available, and the tests were carried out immediately after a previous water experiment. The possible antidiuretic hormone content and its stability were then quite unknown.

Some experiments were also carried out with the serum of the acromegalic patient and that of a normal control of the same sex and age.

Results

Twenty-three experiments on the water excretion were carried out. Seven of them are presented in the following tables and curves, the remaining experiments, producing similar results, are only briefly recorded in the following paragraphs. The experiments on the effect of the subcutaneous injection of sera, on the water excretion, are also not mentioned in detail, as the results were negative.

The amount of the urine excreted hourly by a normal rabbit under normal conditions, as well as its concentration of solids and chlorine ions, are not always constant. The amounts of urine excreted hourly in the beginning of our experiments varied between 1.5 and 3.8 c.c. The specific gravity was, in the most cases, about 1.050 (between 1.043 and 1.056). Only in experiment A, when the amount of urine was very small (1.5 c.c.), was the specific gravity as high as 1.110. The concentration of chlorine ions varied between 0.94 and 3.01 mg. per c.c. urine; only in the experiment A was the concentration much higher (7.65 mg.). The oral administration of 150 c.c. tap-water was always followed by an increased excretion of urine for some three to five hours (Fig. 2). With the exception of experiment O, where a considerable part of the water was retained in the tissue, this excretion happened promptly. The increased urine elimination was always accompanied by a considerable decrease in the concentration of the solids and the chloride ions (Fig. 2). Therefore, the absolute amounts

of excreted solids and chlorine ions were increased to a less extent than was the volume of eliminated water. (Control experiment, A.I.O.)

When 1/200 unit of pitressin was subcutaneously injected simultaneously with the oral administration of water, the water elimination was delayed (experiment R), (Fig. 5). Even after seven hours it was not completely finished. Further, a considerable increase of the chlorine ion output and a certain increase of the output of the solids was observed. The excretion

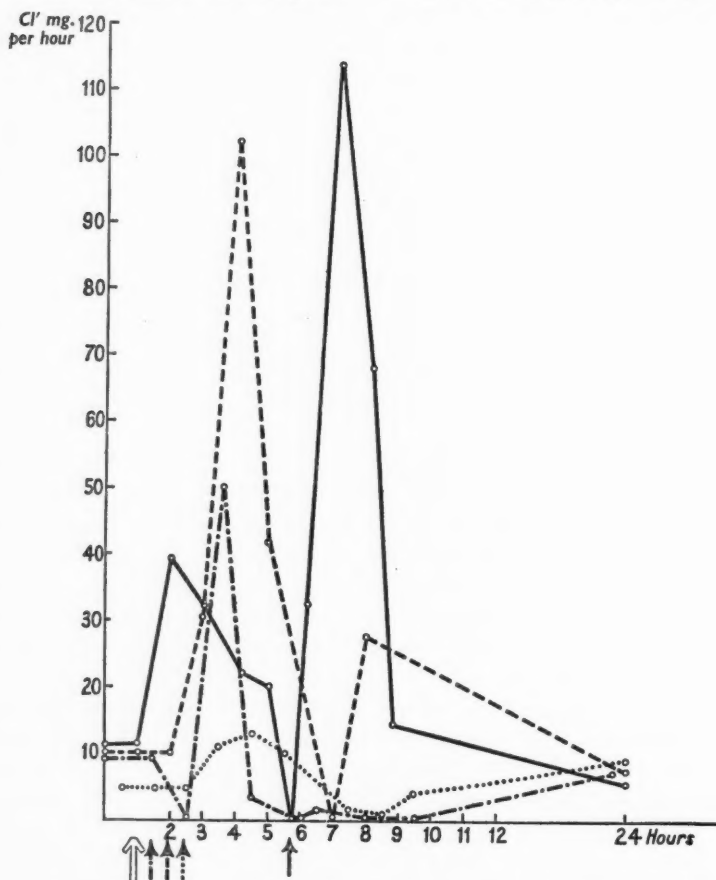


FIG. 3. To show the effect on chloride excretion of the subcutaneous injection of cerebrospinal fluid of the acromegalic patient (and the effect of radiation of the pituitary gland), and of a normal control woman of the same age. 150 c.c. of water were given per os at the same time (and with the first experiment 150 c.c. of water had also been given five hours previously—indicated by double arrow ↑).

Ordinates—Chloride excretion expressed as Cl' mg. per hour.

Abscissae—hours.

— Acromegalic, 1st collection, January 22, 4 c.c., experiment A.
 - - - - - " 2nd collection, February 4, 8 c.c., experiment K.
 - . - . - . " 3rd collection, March 12, 8.5 c.c., experiment P.
 Normal control, 8 c.c., experiment L.

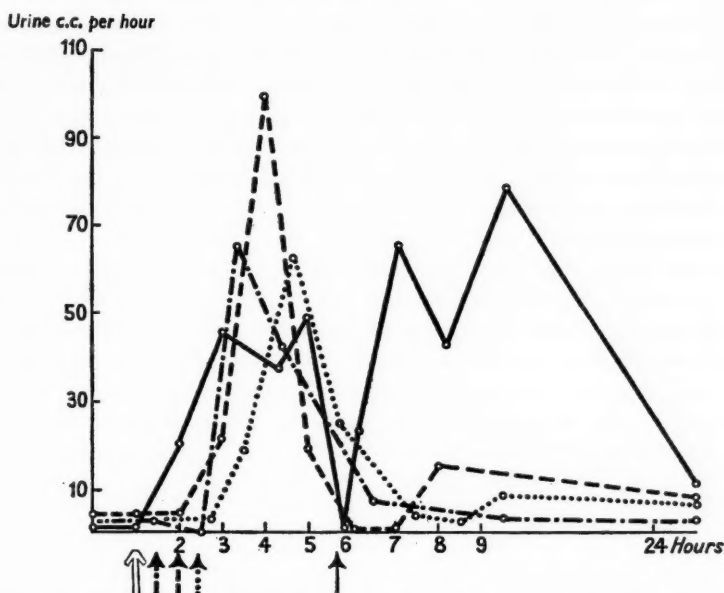


FIG. 4. Effect on excretion of urine of the subcutaneous injection of cerebrospinal fluid of the acromegalic patient (and the effect of radiation of the pituitary gland), and of a normal control woman of the same age. 150 c.c. of water were given per os at the same time (and with the first experiment 150 c.c. of water had also been given five hours previously—indicated by double arrow \Uparrow).

Ordinates—urine excretion c.c. per hour.

Abscissae—hours.

— Acromegalic, 1st collection, January 22, 4 c.c., experiment A.
 - - - - - " 2nd collection, February 4, 8 c.c., experiment K.
 " 3rd collection, March 12, 8.5 c.c., experiment P.
 Normal control, 8 c.c., experiment L.

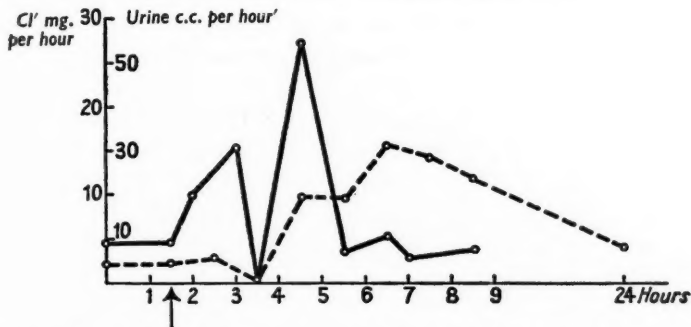


FIG. 5. To show the effect of a subcutaneous injection of 1/200 unit of pitressin on urinary and chloride excretion of a rabbit; 150 c.c. of water were given per os at the same time. Experiment R.

Ordinates—Cl' mg. per hour, e.g. 10; urine excretion c.c. per hour, e.g. 10.

Abscissae—hours.

— chloride. - - - - - urine.

of the chlorine ions was increased to a much greater extent than the water elimination (Fig. 5). The subcutaneous injection of larger doses of pitressin (1/25 to 1/100 unit) caused a longer delay of the diuresis and a greater increase of the chlorine elimination.

When the spinal fluid of a healthy person was injected, together with the oral administration of water (experiment L), the course of the normal water diuresis, with the elimination of a large amount of urine of low concentration of solids and chlorine, was in no way changed (Figs. 3, 4).

When the spinal fluid of the acromegalic patient was subcutaneously injected—4 c.c. of the first collection, 8 c.c. of the second, and 8.5 c.c. of the third collection respectively—(together with the oral administration of water), there was no considerable delay of the diuresis (Fig. 4). However, a considerable increase of the elimination of chlorine ions was observed both absolutely and relatively in experiments A and K, and relatively in experiment P (Fig. 3). The elimination of the solids was not characteristically influenced. The effect of the 4 c.c. in experiment A was nearly the same as that of 8 c.c. in experiment K, and much more intense than the effect of the 8.5 c.c. in experiment P (Fig. 3).

The subcutaneous injection of 30 c.c. of serum from a healthy person had a slowly delaying effect on the urine elimination, but no influence on the concentration of the solids and the chlorine ions. The injection of 30 c.c. of serum of the acromegalic patient had the same effect as that of the healthy person.

Discussion

The essential feature of the rabbit experiments was the very definite influence of the acromegalic's spinal fluid on chloride excretion, whereas the spinal fluids of the normal control patients were without effect. Subcutaneous injections of the spinal fluid of the acromegalic patient (M. R.) produced a relative (nearly always) and an absolute (always) increase in the elimination of chlorine ions in the rabbits' urine. The effect was relatively at its highest in the spinal fluid of the first collection (22nd January), lower in that of the second collection (4th February), and at its lowest in that of the third collection (12th March). This diminution of chloride effect corresponded with the clinical improvement that appeared to follow radiation therapy. At the same time the patient's water balance tended to become normal (Fig. 1). From 11th January to the 20th, a period preceding the first and second lumbar punctures, the average daily fluid intake was 1461 c.c. and urinary output 876 c.c. (the discrepancy being partly explained by the excessive perspiration), whereas after the second lumbar puncture (4th February) the average daily fluid intake and output was of the same order, about 1400 c.c.

In addition to the increased elimination of chlorides, the standardized pitressin (P. D. & Co.) produced the characteristic delay in diuresis

(Fig. 5). The latter effect was not, however, brought about by the acromegalic patient's spinal fluid. A quantitative comparison of the chloride effect of pitressin and the acromegalic's spinal fluid shows that 1 c.c. of the spinal fluid of the first collection contains a pitressin equivalent of about 1/800 unit, of the second collection 1/1500 unit, and of the third collection 1/3000 unit. The antidiuretic effect of 1/200-1/400 unit of pitressin is small but clearly observable, and as these amounts were contained in the total quantity of acromegalic spinal fluid used in each experiment, we should have detected an antidiuretic effect if such were present. Two possible explanations of the apparent absence of the antidiuretic effect are (1) that some substance present in the spinal fluid obscured the antidiuretic action; (2) that the hormone producing the increased chloride excretion is different from the antidiuretic hormone. This latter supposition is not in keeping with the numerous experiments carried out on extracts of the posterior pituitary gland. It is also recognized that the antidiuretic effect of the hypophysis is much less constant than the effect on the chloride excretion (Fromherz (2)). We conclude that the spinal fluid of the acromegalic patient (M. R.) contained a recognizable amount of a hormone of the pituitary posterior lobe, which could be found neither in the spinal fluid of a normal person, nor in the serum of the patient.

Summary

A spinster, aged 32, with well-developed acromegaly, was observed to excrete less fluid than she drank and to perspire freely. Subcutaneous injections of her cerebrospinal fluid into rabbits after the oral administration of water, resulted in an increased excretion of chlorides, comparable to that observed with pitressin, but in no appreciable delay in fluid excretion. Cerebrospinal fluid from control normal patients, and sera from the acromegalic and control patients, had no influence on chloride or water excretion. The experiments indicated the presence of measurable quantities of pituitary antidiuretic hormone in the cerebrospinal fluid of this acromegalic patient and that the amount of hormone decreased simultaneously with the clinical improvement following radiation of the pituitary region.

One of the authors (P. E.) takes this opportunity of expressing his indebtedness to the Society for the Protection of Science and Learning (formerly the Academic Assistance Council, London), for a Research Fellowship, and to the Lister Institute of Preventive Medicine, London, for a personal grant, and for its hospitality.

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EXPERIMENT A. 22.1.1936

Rabbit, female, 2,630 grm. Food: Cabbage until 17.0 p.m. 21.1.1936, then oats.						
Time.	Urine excr. per hr. in c.c.	Cl' per c.c. urine in mg.	Cl' excr. per hr. in mg.	Sp.W. 18°.	(Sp.W. - 1) × urine amount per hr.	Remarks.
10.05	1.5	7.65	11.5	1.110	0.165	10.45: 150 c.c. tap- water per os.
11.50	20	1.96	39.2	1.043	0.830	
12.50	46	0.70	32.2	1.008	0.368	
14.07	36	0.63	22.7	1.007	0.252	
14.50	48	0.42	20.3	1.009	0.432	
15.30	0	—	—	—	—	15.30: 150 c.c. tap- water per os. + 4 c.c. acromegalic spinal liquid subcut.
16.10	22	1.47	32.8	1.012	0.264	
17.00	65	1.75	113.8	1.009	0.585	
18.00	42	1.61	67.6	1.07	0.294	
18.35	79	0.21	14.5	1.008	0.632	
23.1.1936 9.30	11	0.84	9.24	1.021	0.231	

EXPERIMENT I. 3.2.1936

Rabbit, female, 2,365 grm. Food: Cabbage until 17.0 p.m. 2.2.1936, then oats.						
Time.	Urine excr. per hr. in c.c.	Cl' per c.c. urine in mg.	Cl' excr. per hr. in mg.	Sp.W. 18°.	(Sp.W. - 1) × urine amount per hr.	Remarks.
10.00	2.7	0.94	2.53	1.056	0.151	10.10: 150 c.c. tap- water per os.
11.10	18	0.91	16.45	1.012	0.216	
12.10	86	0.14	12.08	1.008	0.688	
13.10	0	—	—	—	—	
14.10	0.4	1.12	2.13	1.037	0.070	
15.10	3.4					
17.10	3.9	0.76	2.96	1.040	0.156	
4.2.1936						
10.00	4.3	1.77	7.62	1.048	0.206	

EXPERIMENT K. 5.2.1936

Rabbit, female, 2,474 grm. Food: Cabbage until 17.0 p.m. 4.2.1936, then oats.						
Time.	Urine excr. per hr. in c.c.	Cl' per c.c. urine in mg.	Cl' excr. per hr. in mg.	Sp.W. 18°.	(Sp.W. - 1) × urine amount per hr.	Remarks.
9.30	3.3	1.48	4.88	1.043	0.142	9.50: 150 c.c. tap- water per os + 8 c.c. acromegalic spinal liquid subcut.
10.50	21	1.47	30.85	1.014	0.294	
11.50	100	1.02	102.0	1.009	0.900	
12.50	19	2.18	41.5	1.011	0.209	
13.50	0	—	—	—	—	
14.50	0	—	—	—	—	Weight: 2,420 grm.
15.50	16.4	1.58	27.6	1.024	0.393	
6.2.1936 10.00	7.2	1.02	7.3	1.032	0.231	
17.10	6	2.52	15.3	1.040	0.240	

URINARY EXCRETION OF CHLORIDES

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EXPERIMENT L. 7.2.1936

Rabbit, female, 2,425 grm. Food: Cabbage until 17.0 p.m. 6.2.1936, then oats.

Time.	Urine excr. per hr. in c.c.	Cl' per c.c. urine in mg.	Cl' excr. per hr. in mg.	Sp.W. 18°.	(Sp.W.—1) × urine amount per hr.	Remarks.
9.45	3.3	1.43	4.74	1.049	0.162	9.55: 150 c.c. tap- water per os+8 c.c. spinal liquid (healthy person) subcut.
10.55	18	0.56	10.1	1.022	0.396	
11.55	62	0.21	13.0	1.007	0.434	
12.55	25	0.38	9.65	1.009	0.225	
13.55	0	—	—	—	—	
14.52	5.2	0.25	1.27	1.028	0.146	
15.52	2	0.28	0.56	1.032	0.064	
16.55	8	0.49	3.92	1.036	0.288	
8.2.1936						
10.00	2.7	3.46	9.38	1.045	0.122	Weight: 2,450 grm.

EXPERIMENT O. 17.2.1936

Rabbit, female, 2,495 grm. Food: Cabbage until 17.0 p.m. 16.2.1936, then oats.

Time.	Urine excr. per hr. in c.c.	Cl' per c.c. urine in mg.	Cl' excr. per hr. in mg.	Sp.W. 18°.	(Sp.W.—1) × urine amount per hr.	Remarks.
10.05	2.7	1.89	5.1	1.056	0.152	10.15: 150 c.c. tap- water per os.
11.15	0	—	—	—	—	
12.15	35	0.42	14.7	1.011	0.385	
13.15	22	0.49	10.8	1.009	0.198	
14.15	16	0.77	12.3	1.013	0.208	
15.15	3.2	0.42	1.34	1.023	0.074	
16.15	0.9	0.28	1.31	1.027	0.127	
17.15	8.4					
18.2.1936						
10.15	4.4	1.96	8.6	1.038	0.167	Weight: 2,630 grm.

EXPERIMENT P. 19.2.1936

Rabbit, female, 2,590 grm. Food: Cabbage until 17.0 p.m. 18.2.1936, then oats.

Time.	Urine excr. per hr. in c.c.	Cl' per c.c. urine in mg.	Cl' excr. per hr. in mg.	Sp.W. 18°.	(Sp.W.—1) × urine amount per hr.	Remarks.
10.00	3	3.01	9.03	1.047	0.141	10.05: 150 c.c. tap- water per os+8.5 c.c. acromegalic spinal liquid subcut.
11.05	0	—	—	—	—	
12.05	65	0.77	50.0	1.014	0.620	
13.05	42	0.07	2.94	1.008	0.336	
15.05	7.2	0.07	0.50	1.015	0.107	
17.05	2.8	0.14	0.40	1.035	0.098	
18.05	2.8	0.21	0.59	1.041	0.105	
20.2.1936						
10.00	3	2.54	7.6	1.038	0.114	Weight: 2,605 grm.
17.30	4.5	3.99	17.9	1.045	0.202	

EXPERIMENT R. 24.2.1936

Rabbit, female, 2,660 grm. Food: Cabbage until 17.0 p.m. 23.2.1936, then oats.

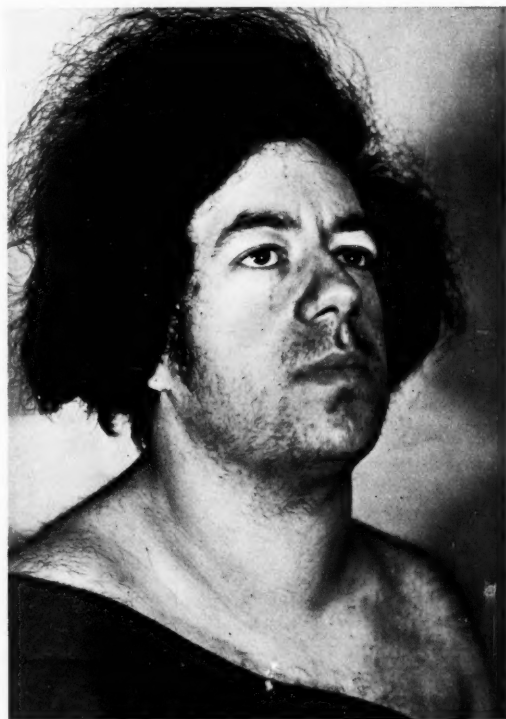
Time.	Urine excr. per hr. in c.c.	Cl' per c.c. urine in mg.	Cl' excr. per hr. in mg.	Sp.W. 18°.	(Sp.W.—1) × urine amount per hr.	Remarks.
10.40	3.8	1.12	4.26	1.045	0.171	10.40: 150 c.c. tap- water per os 1/200 unit pitressin subcut.
11.40	6	2.6	15.6	1.026	0.156	
12.40	0	—	—	—	—	
13.40	18	1.54	27.8	1.026	0.360	
14.40	18	0.21	3.8	1.008	0.144	
15.40	32	0.18	5.8	1.012	0.384	
16.40	28	0.063	1.76	1.009	0.252	
17.40	24	0.14	3.4	1.009	0.216	
25.2.1936						
10.00	8	2.07	16.6	1.032	0.280	Weight: 2,660 grm.



Aged 14



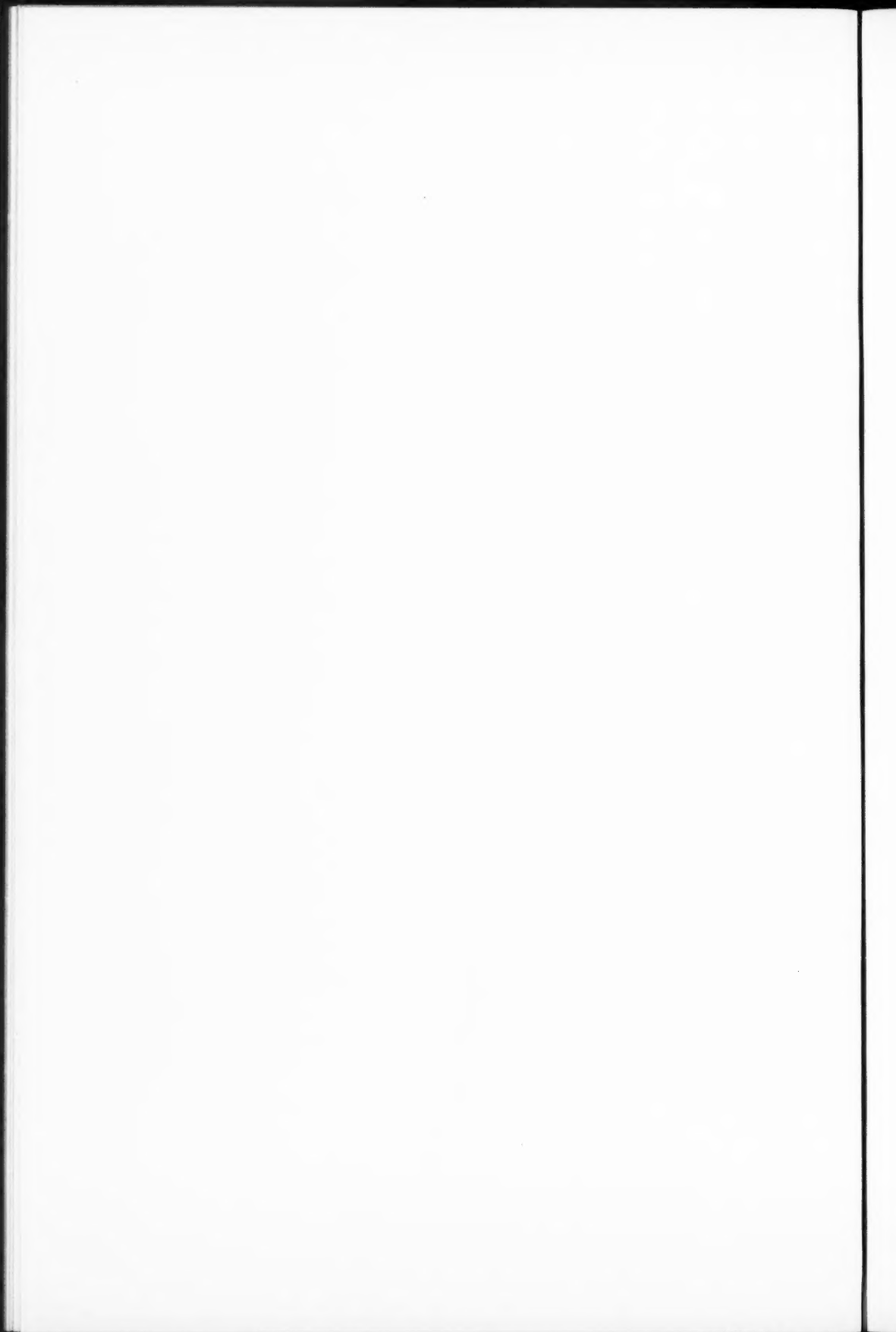
Aged about 20



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Aged 32



CHRONIC NON-LEUKAEMIC MYELOSIS¹

By R. A. HICKLING

(From Charing Cross Hospital)

With Plates 8-9

MANY cases have been described of patients with massive enlargement of the spleen due to myeloid metaplasia, in whom examinations of the circulating blood have not revealed the characteristic blood picture of myeloid leukaemia.

Some of these cases have been regarded as closely related to chronic leukaemic myelosis (chronic myeloid leukaemia), and have been described as cases of 'aleukaemic' or 'sub-leukaemic' myelosis; others have been regarded as quite distinct from that disease, and have been described under several different names, according to the views of the authors regarding the nature of the condition. A discussion of the problems presented by patients with massive myeloid splenomegaly will therefore involve reference to both groups of cases, and for convenience the term 'chronic non-leukaemic myelosis' is used in this paper to refer to all patients who present massive enlargement of the spleen due to myeloid metaplasia, in whom the characteristic blood picture of leukaemic myelosis is not found. The reason for the choice of this name is given later.

Patients who present the features of chronic non-leukaemic myelosis, in the sense used here, usually also have enlargement of the liver, no clinical enlargement of the lymphatic glands, a moderate or sometimes severe anaemia, and a normal or moderately raised total leucocyte count, the differential count showing the presence of immature red and white cells.

Anaemia may be absent at some stages of the illness; in some cases immature cells have not been constantly present in the circulating blood, in others nucleated red cells have been present, but no myelocytes. In a few cases leucopenia has been found.

In view of the similarity of the clinical and histological findings in cases of chronic non-leukaemic myelosis to those of chronic leukaemic myelosis, it is necessary to consider the grounds upon which some authors have maintained a distinction between their cases and the latter disease. These are mainly the differences in the blood picture; and the conception that the myeloid metaplasia of the spleen and other organs is secondary to hypothetical or demonstrated changes in the bone-marrow of a destructive nature.

With regard to the differences in the blood picture, prior to 1905 patients with enlargement of the spleen, in whom examination of the circulating blood revealed the presence of immature red and white cells, but without

¹ Received December 14, 1936.

the very great increase in the total number of leucocytes characteristic of leukaemia, were described under such titles as 'leukanaemia' (Leube and Arneth (41)), 'chronic splenomegaly with anaemia and myeloid reaction of the blood' (Émile-Weil and Clerc (16)), 'splenomegaly of myeloid type without myelocythaemia' (Rathery (59)), 'myeloid splenic anaemia' (Vaquez and Aubertin (68)). In 1905 Hirschfeld (32), pointed out that the essential basis of these cases was myeloid metaplasia, similar to that which occurred in myeloid leukaemia, and suggested that they should be grouped with that disease, and used the name 'atypical myeloid leukaemia'. He maintained that the absence of a high total leucocyte count in these cases, and the high percentage of nucleated red cells in the circulating blood which some of them showed, did not justify separation from myeloid leukaemia, in view of the similar clinical and histological findings. Hirschfeld further maintained this view in 1911 (33) and (1914) (34), using the name 'aleukaemic myelosis'. He states that Schridde in 1910 first proposed the names leukaemic myelosis, and aleukaemic myelosis, to describe cases with the clinical and histological features of myeloid leukaemia, according to whether the blood picture was 'leukaemic' or the total leucocyte count was not greatly raised, respectively. Hirschfeld's views were generally accepted, for after the publication of these papers the older names were not used, and most authors used the word 'myelosis' in describing their cases, to indicate the histological basis of the condition they were considering, and its relation to leukaemic myelosis.

In some recent papers the view has been taken that some of the cases which come within the definition of chronic non-leukaemic myelosis, as used in this paper, are essentially different from 'aleukaemic and leukaemic myelosis'. Ballin and Morse (3), under the title 'myelophthisic splenomegaly', describe two patients with greatly enlarged spleens which were removed at operation. Histological studies of both spleens revealed some fibrosis, with intense myeloid metaplasia, a feature of which was the presence of large numbers of giant cells identical with bone-marrow giant cells. The blood of both patients contained immature red and white cells, and X-rays of the bones showed normal marrow spaces. The authors assume that the bone-marrow is not functioning, that blood-cell formation is occurring in the spleen and elsewhere, and choose the name 'myelophthisic splenomegaly' on this assumption. No evidence is advanced to support the assumption. Vaughan (70) describes three similar cases under the title 'Myelosclerosis'. However, in the patient which came to autopsy, marked myeloid transformation of the bone-marrow was present, in addition to myeloid metaplasia of the liver and of a spleniculus. (The spleen of this patient had been removed seven years previously.) Most cases with the same clinical findings, blood picture, and histological appearances as these cases of 'myelophthisic splenomegaly' and 'myelosclerosis' have been found to have hyperplastic bone-marrow, including the one case in Vaughan's paper which came to autopsy.

A notable exception to this is one of the three cases described by McMichael and McNee (46) under the title 'leuco-erythroblastosis'. No hyperplasia of

the bone-marrow was present, but on the other hand no sign of any sclerosing or ossifying process. In all three cases there was massive splenomegaly due to myeloid metaplasia, and immature red and white cells were present in the circulating blood. In the case that came to autopsy there was myeloid metaplasia of the liver. The authors maintain a distinction between their cases and cases of 'leukaemia', mainly upon the grounds of the difference in the blood picture, and the absence of much diminution in size of the spleens to X-ray treatment. With regard to the latter point, this absence of much diminution in size of the spleens to X-ray treatment has been observed in several cases diagnosed, following complete post-mortem examination, as cases of 'aleukaemic myelosis', for example, one described by Levy (42). It has also been observed repeatedly that X-ray treatment does not have much effect upon the blood picture of cases of 'aleukaemic myelosis'. Schwarz (64) points out that X-ray treatment converts 'leukaemic myelosis' into 'aleukaemic myelosis', and implies that therefore the treatment might not be expected to have much effect upon the blood picture of a patient who was already 'aleukaemic', that is to say, who had a low total leucocyte count and only a small percentage of immature cells before treatment was given.

Many cases of chronic non-leukaemic myelosis have had a very chronic course, without much interference with the patient's general health. In some the myeloid metaplasia has not affected all the organs and tissues which may show this change in typical cases of leukaemic myelosis. But these features cannot be held to show that these cases are essentially different from leukaemic myelosis, for Naegeli (49) states that leukaemic myelosis may last twenty years, though cases with a normal or only slightly raised total leucocyte count, and few immature cells, as a rule have a better prognosis than cases with a typical leukaemic blood picture. Hirschfeld (34) states that typical cases of chronic leukaemic myelosis may not show myeloid metaplasia of all the organs.

The problem of the association of proved changes in the bone-marrow of a sclerosing or ossifying nature with myeloid metaplasia of the spleen and other organs is discussed later.

Most of the patients in which these changes have been found, either at autopsy, or by means of radiological examinations of the skeleton, have appeared clinically as cases of massive splenomegaly with immature red and white cells in the circulating blood, but without a very great increase in the total numbers of circulating leucocytes. The most striking feature has been the massive splenomegaly, due to myeloid metaplasia, similar to the spleens of cases of chronic leukaemic myelosis. It appears to the present writer that as long as the cause of chronic leukaemic myelosis remains unknown, all cases which present this massive myeloid splenomegaly, whether in association with 'myelosclerosis' or 'osteosclerosis', or not, should be studied together, and in relation to chronic leukaemic myelosis, as this will facilitate the study of myeloid metaplasia of the spleen and other organs,

and throw light upon the nature of leukaemic myelosis. Therefore, the use of names which bear no relation to the underlying condition of myeloid metaplasia should not be used, as interest is thereby diverted from the main characteristic of the cases, namely, massive myeloid splenomegaly.

The name 'chronic non-leukaemic myelosis' was used as an alternative title by Mavros (45) in describing a case of 'aleukaemic myelosis with osteosclerosis'. It is chosen as the title for the present paper, since it clearly expresses the view that the most important feature of the cases considered is 'myelosis', or myeloid metaplasia. The term 'aleukaemic myelosis' is used by some authors in the restricted sense of applying only to cases in which the circulating blood contains no immature cells at all, for example, by Jaffé (38) and by Naegeli (49), in one part of his book (page 445). It is therefore not a suitable name for the whole group of cases. The name 'sub-leukaemic myelosis' also appears to be unsuitable, since it suggests that the blood picture is not quite sufficiently striking to justify the use of the name 'leukaemic myelosis'; but many of the cases have a low total leucocyte count, and a very low percentage of immature cells.

The diagnosis of chronic non-leukaemic myelosis depends upon the finding of immature red and white cells in the circulating blood, without the great increase in the total number of leucocytes characteristic of leukaemia, in a patient with massive enlargement of the spleen. In a few cases immature red and white cells have been entirely absent, but in most of these the patient was under observation only for a short time. Jaffé (38) takes the view that the diagnosis of 'aleukaemic myelosis' should only be made when no immature leucocytes are present in the circulating blood. Yet of the many references given in his paper, in only three cases—those of Donhauser (13), Hirschfeld (31), and Berblinger (6)—were no immature cells present. Reference to cases in which no immature cells were found in the circulating blood is made in considering the effects of splenectomy.

In any case of very severe anaemia both nucleated red cells and myelocytes may be found in the circulating blood. Therefore, in such cases the presence of immature cells would not necessarily indicate that splenic enlargement was due to myeloid metaplasia. But most cases of chronic non-leukaemic myelosis have not a severe grade of anaemia.

There are two procedures which may help in settling the question whether splenic enlargement is due to myeloid metaplasia, namely, splenic puncture, and blood examinations after injection of adrenalin.

Splenic puncture was advocated by Hirschfeld in 1914 (34), and has been used by numerous observers, to assist in ascertaining the cause of splenic enlargement, for example in tropical splenomegalies. It has frequently been used in cases of chronic non-leukaemic myelosis, to demonstrate myeloid metaplasia of the spleen. In most of the cases, however, the peripheral blood contained immature red and white cells—for example, that of Levy (42)—so that the diagnosis was usually not in doubt prior to the

puncture. Carnot, Caroli and Busson (9) published two cases of 'aleukaemic hepato-splenic myelosis' diagnosed by splenic puncture, the fluid withdrawn from the spleen containing numbers of nucleated red cells and myelocytes. In their first case the circulating blood in 1931 contained no immature cells, but no differential count is given; in 1935 the patient was seen again, having relapsed following improvement effected by X-ray treatment; on this occasion no myelocytes were found in the blood, but 2 per cent. of nucleated red cells, with a severe anaemia. In their second case no differential counts are given, but they state that no myelocytes or nucleated red cells were found. After adrenalin injection the peripheral blood of this case presented 5.8 per cent. of myelocytes and 0.6 per cent. nucleated red cells. Adrenalin injections were also used by Olmer and Paillas (52); but in their case the blood before adrenalin injection contained 8 to 10 per cent. of myelocytes, and 12 to 13 per cent. of nucleated red cells.

Adrenalin injections have not been used in any of my cases. In two of them (Nos. 3 and 5) splenic puncture was performed; but the differential count of the fluid obtained differed very little from that of the circulating blood, which contained small numbers of immature cells constantly.

Cases of chronic non-leukaemic myelosis have frequently been wrongly diagnosed as splenic anaemia or Banti's disease. The importance of this mistake is emphasized when considering the results of splenectomy in cases of chronic non-leukaemic myelosis. It is generally agreed that immature red and white cells do not occur in the blood in patients with these diseases, and writers lay stress upon this point, for example, Banti (4) and Osler (53). Osler found that only one of his 13 cases of splenic anaemia presented young cells in the blood, 1.5 per cent. myelocytes, and 45 nucleated red cells among 300 leucocytes. This patient made a good recovery. But in his subsequent paper of 1902 (54) he states that the patient was re-admitted five months after leaving hospital, and died of profound anaemia, and that she did not belong to the same group as the other cases. No notes of the histology of the organs of this case is given. More recently Chaney (10) reviewed 69 cases of splenic anaemia, and he states that no abnormal red or white cells were noted.

Rarely the occurrence of metastatic deposits of malignant growths in the bone-marrow is accompanied by myeloid metaplasia of the spleen and liver, and the spleen may consequently become enlarged. Such cases have been reported by Epstein (18), Frese (25), Askanazy (1), Parmentier and Chabrol (55), Hirschfeld (34), Martin, Dechaume and Ben Rais (44). In all of these, except that of Epstein, myeloid metaplasia of the spleen was demonstrated, and immature red and white cells were present in the circulating blood of all except that of Askanazy, but no blood counts of this case are recorded. Though the occurrence of immature cells and white cells in the circulating blood in cases of carcinomatosis of the bone-marrow has been well-known for many years (it is mentioned in Émile-Weil and Clerc's paper of 1902 (16)), cases in which there has also been myeloid

TABLE I

27 Cases of Non-leukaemic Myelosis upon which Splenectomy was Performed

Reference.	Chief characteristics of blood before operation.	Result of splenectomy.	Chief characteristics of blood after operation.	Histology of spleen and of other organs if examined.
Rathery, 1902. (59)	L. 41,400. My. 1-33%. NR. 0.	Died in 24 hours.	Not noted.	Spleen. Myeloid metaplasia of pulp. Malpighian bodies preserved. Liver. Myeloid metaplasia. Bone-marrow. Hyperplasia.
Hirschfeld, 1905. (31)	L. 8,300-20,600. No detailed differential count. Lymphocytes to polymorphs, 40:60.	Died in 24 hours.	Not noted.	Spleen. Myeloid metaplasia. Lymph glands. Myeloid metaplasia. Bone-marrow not examined.
Nauwerck and Moritz, 1905. (51)	L. 7,000. My. 4-68%. NR. 7%.	Died in 4 weeks.	Leucocytosis with a fall in myelocytes. NR. 46%.	Spleen. Myeloid metaplasia. Liver. Myeloid metaplasia.
Rychlik, 1907. (61)	L. 14,300-15,600. My. 1-22-3-8%. NR. 0-0-5%.	Died in 24 hours.	L. 25,600-31,280. My. 0. NR. 0-0-9%.	Spleen. Myeloid metaplasia. Liver. Myeloid metaplasia. Bone-marrow. Hyperplasia.
Hirschfeld, 1914. (34)	L. 8,900-19,000. My. 0-5%. NR. 'present'.	Died in 3 hours.	Not noted.	Spleen. Myeloid metaplasia. Liver. Myeloid metaplasia. Bone-marrow. Hyperplasia, with sclerosis in places.
Bianchi, 1921. (7)	L. 3,800 } 20 months before My. 0 } operation. NR. 0 } L. 11,800 } 8 months before My. 0 } operation. NR. 0 }	Died in 4 days.	Not noted.	Spleen. Myeloid metaplasia.
Berblinger, 1926. (6)	'No leukaemic blood picture.' 'Slight increase in meta-myelocytes towards the end.'	Died in 2 days.	Not noted.	Spleen. Myeloid metaplasia. Liver. Myeloid metaplasia. Lymph glands. Myeloid metaplasia. Bone-marrow. Hyperplasia.
Fieissinger and Olivier, 1926. (20)	L. 19,000. My. 35%. NR. 'present'.	Died in a few days.	Not noted.	Spleen. Myeloid metaplasia and fibrosis. Malpighian bodies preserved.
Gordon, 1927. (28)	L. 'about 12,000'. My. 'a few'.	Died in 3 days.	'High leucocytosis. Blood flooded with transition forms of leucocytes and nucleated red cells.' L. 8,500-86,000. My. 15-20%. NR. 'many', constantly.	Not noted.
Villa, 1927. (71 and 72)	L. 5,000. My. 0. NR. 'a few'.	Survived 7 years.		Spleen. Myeloid metaplasia. Bone-marrow puncture. Myeloid hyperplasia.

My. 0.
NR. 'a few'.

My. 15-20%.
NR. 'many' constantly.

Bone-marrow puncture. Myeloid hy-
perplasia.

Roch and Mozer, 1927. (60)	L. 12,430. Under observation only 10 days before operation. My. 0. NR. 0.	Survived 3 years.	L. 14,260-27,420. My. 8% and constantly present. NR. 1% and occasionally large numbers.	Spleen. Myeloid metaplasia, and atrophy of Malpighian bodies.
Ballin and Morse, Case 1. 1927. (3)	L. 16,000-24,000. My. 2-10%. NR. 8-17%.	Survived 8 years	Blood count remained approximately constant.	Spleen. Myeloid metaplasia.
Case 2.	L. 16,000-24,000. My. 2-10%. NR. 8-17%.	Survived to time of publication, a short time.	L. 52,000. My. 0. NR. 9%.	Spleen. Myeloid metaplasia.
Jaffé, 1927. (38)	Case 1. L. 7,500. My. 0. NR. 2-4%.	Died in 16 hours.	Not noted.	Spleen. Myeloid metaplasia. Malpighian bodies preserved.
Case 2.	L. 4,350. Under observation only 13 days before operation. My. 0. NR. 0.	Died during operation.	Not noted.	Spleen. Myeloid metaplasia. Liver. Myeloid metaplasia.
Dubinskaja, 1928. (15)	L. 23,000. My. 6%. NR. 'present'.	Died in a few days.	Not noted.	Spleen. Myeloid metaplasia.
Pinkerton, 1929. (58)	L. 5,200. My. 6%. NR. 156 per c.mm.	Died in 2½ years.	L. 180,000. My. 83%.	Spleen. Myeloid metaplasia. Malpighian bodies preserved.
Gaudier and Houcke, 1930. (26)	L. 4,900. Under observation only 5 days before operation. My. 0. NR. 0.	Died in 8 days.	Not noted.	Spleen. Myeloid metaplasia and fibrosis. Liver. No myeloid metaplasia. Bone-marrow. Hyperplastic in ribs and tibia.
Downey, Palmer and Powell, 1930. (14)	L. 2,500-3,300. My. 5-12%. NR. 1% and 'numerous'.	Died in 3 months.	L. 10,400. No differential count given.	Spleen. Myeloid metaplasia and fibrosis. Liver (piece removed at operation). Myeloid metaplasia.
Emile-Weil and Sée, 1932. (17)	Not noted. Abdominal mass was found to be spleen at operation.	Died in 8 months.	L. 30,000-60,000. My. 5-26%. NR. 6-9%.	Spleen. Myeloid metaplasia. Liver became enormously enlarged after operation.
Fontana and Pettinari, 1933. (24)	L. 7,800. Nature of abdominal mass not certain before operation. My. 0. NR. 0.	Survived 1 year.	L. 8,500-11,000. My. 0-1%. NR. 2-8%.	Spleen. Myeloid metaplasia.

L. = Total leucocytes per c.mm.
My. = Percentage of myelocytes and younger cells.
NR. = Percentage of nucleated red cells.

TABLE I (continued)

Reference.	Chief characteristics of blood before operation.	Result of splenectomy.	Chief characteristics of blood after operation.	Histology of spleen and of other organs if examined.
Favre, Croizat and Guichard, 1934. Case 1. (19)	Chief characteristics of blood before operation. L. 'slight leucocytosis' to 20,000. My. 0, 'slight myeloid reaction at end'. NR. not noted.	Died in 3 days.	Not noted.	Spleen. Myeloid metaplasia. Liver. Myeloid cells in masses. Lymph glands. Myeloid metaplasia.
Case 2.	L. 7,200-8,400. My. 0. NR. 'numerous'.	Survived 3 months.	L. 20,400-30,000. My. 0. NR. not noted.	Spleen. Myeloid metaplasia. Liver (piece removed at operation). Myeloid metaplasia.
Olmer and Paillass, 1935. (52)	L. 7,500-10,800. My. 8-10%. NR. 12-13%.	Died in 2 days.	Not noted.	Spleen. Myeloid metaplasia and reticulo-endotheliosis.
McMichael and McNee, 1936. (46)	L. 8,400-21,300. My. 9-25%. NR. 0-7%.	Died in 2 days.	Not noted.	Spleen. Myeloid metaplasia. Liver. Myeloid metaplasia. Bone-marrow of femur. No sclerosis, no hyperplasia.
Case 2.	L. 2,500-28,000. My. 1-6%. NR. 0.5-3%.	Died in 3 years.	L. 14,000-58,000. My. 0-8%. NR. 45-265%.	Spleen. Myeloid metaplasia.
Case 3.	L. 10,000-36,000. My. 0-3%. NR. 5% and 'present'.	Died in 1½ years.	L. not noted. My. 9%. NR. 8%.	Spleen. Myeloid metaplasia.

L. = Total leucocytes per c.mm.

My. = Percentage of myelocytes and younger cells.

NR. = Percentage of nucleated red cells.

metaplasia of the spleen, with clinical enlargement, would appear to be very rare. Rarely also tuberculosis of the spleen has been accompanied by myeloid metaplasia of the spleen and other organs, and the presence of immature red and white cells in the circulating blood. Swirschewskaja published a case in 1926 (66), and collected others from the literature. These rare cases would therefore come within the definition of non-leukaemic myelosis. The myeloid metaplasia of the spleen and liver cannot be explained on the basis of compensatory blood formation following a destructive process in the bone-marrow, for in most of the cases of carcinomatosis of the bone-marrow no extra-medullary blood formation has been found, and Piney (57) showed that the bone-marrow was hyperplastic around the invading carcinoma cells; this marrow hyperplasia was also demonstrated in one of the cases with myeloid metaplasia of the spleen and liver, that of Parmentier and Chabrol (55). The occurrence of these cases must have an important bearing on the problem of myeloid metaplasia, though it is not possible at present to say what its significance is.

There are two main reasons why the recognition and study of cases of chronic non-leukaemic myelosis are important. The first is that cases have been operated upon for splenectomy, usually in the belief that they were cases of splenic anaemia or Banti's disease, and death has frequently resulted; and the second is that certain special features occur in them, among which are osteosclerosis, and the presence of large numbers of giant cells as part of the myeloid metaplasia, which are much less common in cases of chronic leukaemic myelosis, and a study of these special features may throw light upon the etiology of myeloid metaplasia of the tissues, and upon the nature of chronic leukaemic myelosis.

In Table I are given some details of 27 cases of chronic non-leukaemic myelosis which were submitted to splenectomy. It will be noted that prior to operation either myelocytes, or nucleated red cells, or both, were present in the circulating blood of all cases except eight. In one of these no blood count before operation is given, and in three the period of observation before operation was a few days only. In three of the remaining four the results of the blood examinations, as recorded in the papers, cannot be held to prove the consistent absence of immature cells. In Hirschfeld's case (31) no detailed differential count is given, only the proportion of lymphocytes to polymorphs; in Bianchi's case (7) only two blood counts are given, one performed twenty months and one eight months before operation; in Fontana and Pettinari's case (24) the abdominal mass was not diagnosed as a splenic tumour until operation, and one blood count only is recorded. Of the patients who survived operation for more than a few days, all except two were found to have immature cells constantly in the circulating blood after operation, and in five the total leucocyte count rose considerably, in four to between 52,000 and 86,000 per c.mm., and in one (Pinkerton (58)) to 180,000 per c.mm. Of the two cases in which no immature cells are recorded as present in the circulating blood after operation—in Downey,

Palmer and Powell's case (14)—no differential count after operation is given; in Favre, Croizat and Guichard's case (19) two blood counts after operation are recorded, in neither of which myelocytes occur, but no note is made regarding the presence or absence of nucleated red cells, though these were numerous before operation, in spite of the slight degree of anaemia present.

Of these 27 cases, 15 died within a few days of splenectomy, 1 died in 4 weeks, 1 died in 3 months, 1 died in 8 months, 3 died in $1\frac{1}{2}$ to 3 years; 1 survived 8 years, 1 survived 7 years, 1 survived 3 years, 1 survived 1 year, 1 survived 3 months, 1 survived a short time.

More than half the cases collected from the literature died within a few days of the operation; and in those which survived, the subsequent course of the disease was not beneficially affected by the operation, no striking improvement in the patient's health resulting.

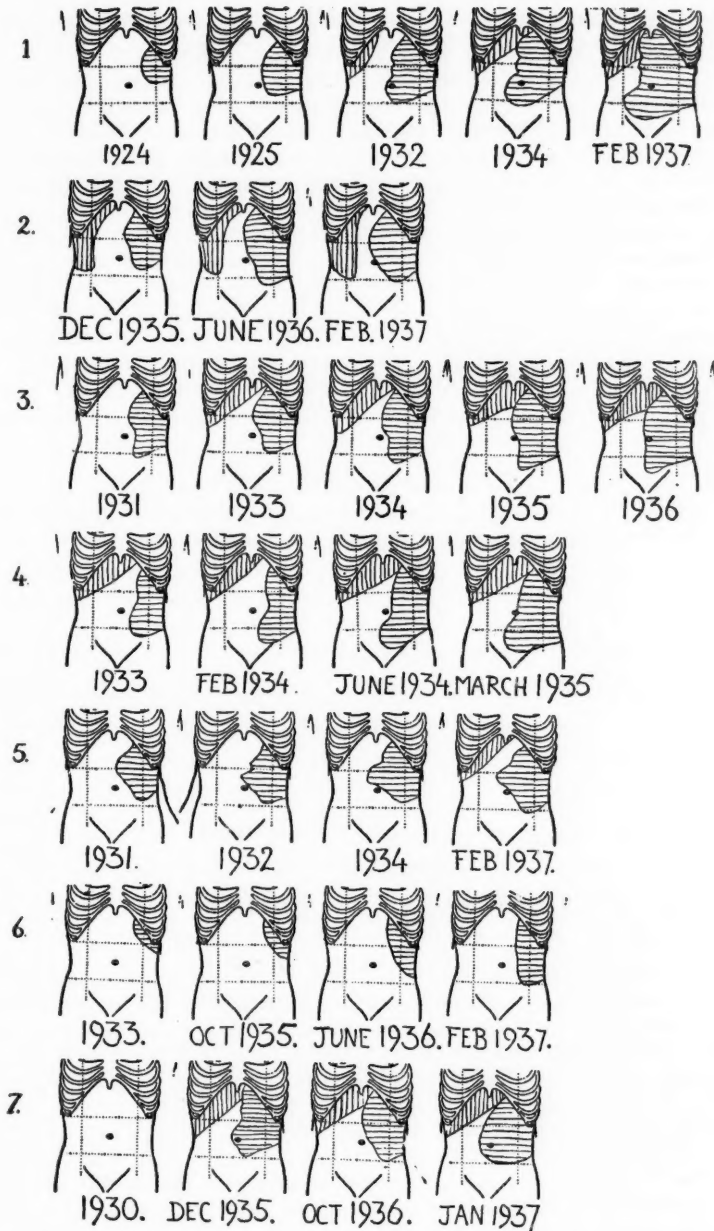
I here present a study of seven cases which I would include under the title, chronic non-leukaemic myelosis. All have been in-patients on at least one occasion at Charing Cross Hospital. I have seen them at intervals of a few months since they first came under my own observation. The features common to all the cases are: (1) A chronic course, varying from 18 months in Case 2, to 13 years and 7 months in Case 1. Both these patients are alive and in very fair health. The shortest period of observation, apart from Case 2, was in Case 4 who died after having been under observation for 2 years. (2) Progressive splenic enlargement, reaching a great size, and enlargement of the liver. (See p. 263.) (3) Absence of enlargement of the lymphatic glands. (4) The constant presence in the blood of immature myeloid cells during the time that they have been under my own observation, with the constant presence of nucleated red cells in some cases, and their presence at some time in all, even in the absence of anaemia.

In all cases the blood Wassermann reaction was negative, and in none was there any family history of splenic enlargement, jaundice, or anaemia.

Clinical Notes

Case 1. Male, present age 70. He complained of abdominal pain in July 1923, and an enlarged spleen was discovered. Blood examination showed mild anaemia, leucocytosis of 16,000 per c.mm. with 28 per cent. of myelocytes. The blood examination was repeated in 1924, twice in 1925, and once in 1926. He then passed out of observation until August 1931, when he was admitted to hospital for operative treatment of haemorrhoids. He has been under observation ever since, and has remained in very fair health, except that during the last twelve months he has had several attacks of perisplentitis.

Case 2. Female, present age 60. She was admitted to hospital complaining of abdominal pain and swelling, and loss of weight, of about two months duration. The abdomen was opened, in the belief that the enlarged spleen was a carcinoma of the stomach. In addition to the enlarged spleen, the liver was found to be enlarged; a spleniculus was removed for



Showing size of liver and spleen at different periods in the seven cases. Copied from drawings made at the time of examination.

histological examination, a report upon which is given later. The blood had not been examined prior to the operation. She made a good recovery from the operation, and is in fair health at the present time.

Case 3. Female, died at the age of 64 in 1936. Since 1917 she had suffered from occasional epistaxis and spontaneous bruising. A severe epistaxis occurred in August 1929, and again in August 1930, and she was brought to hospital by ambulance in this last attack. An enlarged spleen was discovered. She was under close observation from that time, and remained in very fair health, except for discomfort due to the enlarged spleen, and occasional epistaxis and spontaneous bruising. In 1934 and 1935 she developed severe arthritis affecting the hands and feet; a very severe attack occurred in January and February 1936, and the blood uric acid was found to be 16 mg. per 100 c.c. She had never previously suffered from gout, nor was there any family history of this. No relief was afforded by medicinal or dietetic treatment. In March 1936 the splenic pedicle was ligated, in the hope that this would diminish apparently excessive leucocyte destruction, without the danger to the patient's life which splenectomy entailed. A small piece of the liver and of the spleen were removed at operation for microscopical examination. The patient died twenty-four hours after the operation. At post-mortem examination no sign of haemorrhage or thrombosis could be found, and no other condition which might have caused death. An account of the histological findings is given later.

Case 4. Female, died at the age of 56 in 1935. She was admitted to hospital in August 1933 following a haematemesis. She had noticed pain and a 'lump' in the left side of the abdomen for several years. This was found to be a greatly enlarged spleen. She died in July 1935 after several weeks of high fever, bleeding from the mouth and rectum, with the development of a rash consisting of raised pink patches all over the body, especially the abdomen. The histological findings are given later.

Case 5. Female, present age 66. She had a haematemesis in January 1931, and an enlarged spleen was found. She was admitted to hospital for investigation in May 1931, and has been under observation since that time. Her only complaint was discomfort due to the enlarged spleen, and she was in very fair health for a patient of 66. This is the only patient in the present series who presents abnormal pigmentation of the skin; this has been present all her life, and may be associated with the presence of a nodular goitre.

Case 6. Male, present age 51. He had had gripping pains in the left side of the abdomen for thirteen years, and was admitted to hospital in October 1933 for investigation. An enlarged spleen was found, with a mass lying below it. At operation the mass was found to be a large retroperitoneal haematoma, which was drained. No pains have been noticed since the operation, but the spleen has gradually increased in size. At the present time the patient enjoys robust health, and is doing heavy work. His complexion is ruddy with a faint yellow tinge, associated with the constantly high value of the indirect van den Bergh reaction of the blood. The case was published by MacLeod (43) as a case of retroperitoneal haematoma. Before and after operation the blood examination showed the presence of a high leucocytosis, and no abnormal red or white cells were noted. Since October 1935 he has been under the observation of the writer. Repeated blood examinations have shown the constant presence of myelocytes in percentages of 2.5 to 4, and nucleated red cells have been present in most

of the counts. The leucocytosis observed before the operation in 1933 has persisted ever since.

Case 7. Female, present age 57. She was seen in the out-patient department in January 1930, complaining of dyspnoea and spontaneous haemorrhages in the skin. The spleen was not palpated, and blood examination revealed no abnormality. She enjoyed good health until December 1935, when she was seen again in the out-patient department complaining of weakness, loss of weight, and abdominal pain. A large spleen was found. The blood examination showed the presence of a high leucocytosis, 60,000 leucocytes per c.mm., of which 20 per cent. were myelocytes and myeloblasts. She greatly improved in health after X-ray treatment, and is in very fair health at the present time. The chief findings in these seven cases are summarized in Table II.

The Special Features of these Cases

In all the cases myeloblasts have been present in most of the differential counts, even in Cases 3 and 6 in which the percentage of immature leucocytes never exceeded 3.5 and 4.0 respectively (immature leucocytes include myelocytes or younger cells). Megakaryocytes have been present in small numbers in some of the counts in all cases except Case 3. Eosinophile and basophile myelocytes have been found in small numbers at times in some of the cases, but the majority have been neutrophile myelocytes. In all cases the majority of the mature leucocytes were neutrophile polymorphs; and in Cases 3 and 6, in which occurred leucocytosis but very few immature cells, the neutrophile polymorphs accounted for 80-90 per cent. of all the leucocytes.

There has been eosinophilia and basophilia at times in all cases except Case 4. For example, the percentage of eosinophils has been 5 per cent. or more at times in all cases except Cases 4 and 7, and has been 7 per cent. or more in Cases 2 and 5. The percentage of basophils has been 5 per cent. or more in Cases 1, 2, 3, and 7, and in Cases 2 and 7 has reached a maximum of 13.75 and 19 respectively. This is of interest in view of the fact that the older pathologists, as quoted by Hirschfeld (32), considered the presence of eosinophilia, and especially of basophilia, as important in arriving at a diagnosis of leukaemia.

The results of the blood cell examinations have been remarkably constant, when the long time during which these have been carried out is considered. Only in Cases 1 and 7 was there much variation in the total leucocyte count; in Case 1, for the first three years this count varied between 14,000 and 17,000; during the years 1931 to 1935 it remained constant between 5,000 and 8,000; in 1936 it rose to between 31,000 and 64,000, and was 45,000 at the beginning of 1937. In Case 7 there was a marked drop in the total leucocyte count from 60-78,000, to 16,800 following X-ray treatment, and a rise later to 34,000.

The differential leucocyte counts have given results constant within narrow limits in all cases except Case 5. In this case the percentage of

TABLE II. *Summary of the Chief*

Case.	1.	2.	3.
Sex.	M.	F.	F.
Date of 1st symptom.	July 1923.	July 1935.	1917.
Age of patient at that time.	57.	59.	45.
Nature of 1st symptom.	Abdominal pains.	Abdominal pains.	Epistaxis.
Spontaneous haemorrhages.	None before 1934. Purpura since 1934. Increased bleeding from cuts since 1935.	None.	Purpura from 1917 to death. Epistaxes 1917, 1929, 1930, 1935. Haematemesis 1917.
Date when enlarged spleen first found.	July 1923.	Oct. 1935.	Aug. 1930.
Progress of case.	Fairly well till Feb. 1937 except for discomfort due to enormous spleen and perisplenitis.	Fairly well till Feb. 1937. Doing her own house-work.	Died March 1936, after operation for ligature of splenic pedicle.
X-ray treatment.	None until Oct. 1936.	None.	A course in 1930, none since.
X-ray examination of skeleton.	None until July 1936. This shows well-marked 'osteosclerosis'.	None until June 1936. This shows well-marked 'osteosclerosis'.	This showed no notable abnormality, 1932 and 1935.
Test meal analysis.	Low normal.	Not done.	Achlorhydria.
Indirect van den Bergh reaction.	Constantly well above normal limits since 1932. 1932. 5.3 units 1933. 8.0 " 1934. 4.0 " 1936. 2.0 to 4.0 units Feb. 1937. 4.0 units.	1936, four estimations, all within normal limits. Feb. 1937. 1 unit.	Slightly above normal limits, 1932 and 1936.
Blood uric acid estimations in mgm./100 c.c.	Jan. 1936. 7.0 June " 8.7 Sept. " 9.5 Oct. " 8.4 Nov. " 8.3 Feb. 1937. 8.6	June 1936. 4.5 Aug. " 4.7 Nov. " 4.3 Feb. 1937. 5.0	Jan. 1936. 16.0 Mar. " 12.5 Mar. " 15.0
Haemoglobin percentage.	72-88, 1923 to Feb. 1937.	62-70, Oct. 1935 to Feb. 1937.	1930. 40-45 1931. 50 1932 to Mar. 1936, 60-78
Red-blood cells, in millions per c.mm.	3.75-5.0.	3.75-4.5.	1930-1. 3.3-4.0. 1932-6. 3.5-4.5.
White-blood cells per c.mm.	1923. 16,000 1924. 14,000 1925. 16-17,000 1926. 9,000 1931 to Jan. 1936. 5-8,000 June 1936. 15,000 Sept. " 64,000 Oct. " 31,000 Nov. " 46,000 Feb. 1937. 45,000	Oct. 1935 to Nov. 1936. 30-38,000. Feb. 1937. 51,800.	1930-6 constantly 18-35,000.
Percentage of immature leucocytes (My.).	1923-6. My. 17.5-31 NR. 1-3	Oct. 1935 to Feb. 1937. My. 17.25-33.0 NR. 4.0-9.5	1930-6. My. 0.5-3.5 NR. 0.0-1.0
Nucleated red cells (NR.) expressed as percentage of total leucocytes.	1931 to Feb. 1937. My. 11.5-24.25 NR. 1-5		
Percentage of eosinophils (E.).	E. 2.5 or less until Sept. 1936; since then 3.75-5.25.	E. 5.5-7.5.	E. 1.75-6.75, often above 4.0.
Percentage of basophils (B.).	B. 1.5-5.75.	B. 8.0-13.75.	B. 1.5-5.0, usually above 3.0.
Platelets (occasionally counted but usually estimated from blood films)	Constantly low.	Low to normal.	Constantly very high.

Findings in the Seven Cases

4.	5.	6.	7.
F. 1923. 46.	F. Jan. 1931. 60.	M. 1920. 34.	F. 1929. 49.
Abdominal pains. Haematemesis 1933. Epistaxis 1935. Rectal bleeding 1935. Purpura from 1933 to time of death. Aug. 1933.	Haematemesis. Haematemesis 1931. Epistaxes 1934, 1935. Purpura since 1934.	Abdominal pains. Retroperitoneal. Haematoma, operated upon 1933. Purpura 1936.	Purpura. Purpura 1929, 1930, none since.
Died July 1935 after 6 weeks of high fever.	May 1931.	Sept. 1933.	Dec. 1935.
None.	Fairly well till Feb. 1937. Size of spleen causes in- convenience.	In robust health doing heavy work, Feb. 1937.	Fairly well till Feb. 1937.
This showed no notable abnormality, June 1935.	None.	None.	A course in July and August, 1936.
Achlorhydria. Within normal limits, 1933 and 1935.	This showed no notable abnormality, 1931 and 1936. Low normal. Constantly above normal limits since 1931. 1931, slightly above nor- mal. 1933. 5 units 1935. 5 " 1936, above normal. Feb. 1937. 3 units Mar. 1936. 3.6 May " 2.7 Oct. " 5.4 Feb. 1937. 3.3	This showed no notable abnormality, 1936. Not done. 1933-6. 2-3 units. Feb. 1937. 4 units.	This showed no notable abnormality, 1936. Normal. Jan. 1936, above normal limits. Apr. and Oct. 1936, and Feb. 1937, within nor- mal limits.
Not done.	Jan. 1936. 8.7 May " 6.3 Oct. " 7.8 Feb. 1937. 8.0	Jan. 1936. 8.7 May " 6.3 Oct. " 7.8 Feb. 1937. 8.0	June 1936. 4.1 Aug. " 4.4 Oct. " 4.1 Feb. 1937. 4.2
1933. 80 1934. 75 1935. 50	1931. 55-60 1932 to Feb. 1937. 75- 85.	1933. 94 1934. 86 1935 to Feb. 1937. 90- 95. 1933 to Feb. 1937. 5.0- 5.8. Sept. 1933 to Oct. 1936. 20-23,000. Feb. 1937. 18,200.	Jan. to June 1936, 65-70. Aug. 1936. 40. Oct. 1936 to Feb. 1937. 75-85. 4.0-5.0, except Aug. 1936. 2.75. 1930. 7,000 Dec. 1935 to June 1936. 60-78,000. Oct. 1936 (after X-ray treatment) 16,800. Feb. 1937. 34,400.
1933-4. 4.5 1935. 3.5 1933 to Mar. 1935. 30- 50,000. July 1935. 63,000.	1931. 3.5 1932-Feb. 1937. 4.0-4.5. 1931 to Feb. 1937. 5- 11,000.	1933. 94 1934. 86 1935 to Feb. 1937. 90- 95. 1933 to Feb. 1937. 5.0- 5.8. Sept. 1933 to Oct. 1936. 20-23,000. Feb. 1937. 18,200.	Jan. to June 1936, 65-70. Aug. 1936. 40. Oct. 1936 to Feb. 1937. 75-85. 4.0-5.0, except Aug. 1936. 2.75. 1930. 7,000 Dec. 1935 to June 1936. 60-78,000. Oct. 1936 (after X-ray treatment) 16,800. Feb. 1937. 34,400.
1933-5. My. 11.5-20.5. NR. absent in most counts but in others 0.5-1.0.	1931. My. 0.5-4.0 1932. " 7.0-10.0 1933. " 8.5-15.0 1934-5. " 13.0-19.5 1936. " 10.0-15.0 Feb. 1937. " 9.0 NR. absent in many counts, but in others 1-3.	Oct. 1935 to Feb. 1937. My. 1.75-4.0 NR. 0.0-1.5	Jan. 1930. My. 0.0 NR. 0.0 Dec. 1935 to Feb. 1937. My. 10.5-30.0 NR. 0.0-3.0
E. 0.0-1.0.	E. 2.0-7.0, often 5 or more.	E. 1.0-5.75.	Since Dec. 1935. E. 1.5-4.5.
B. 0.5-3.5, often above 2.0. Normal to high.	B. 0.0-3.0, usually be- low 1.0. Constantly low.	B. 1.5-4.5. Constantly high.	B. 5.5-19.0. Normal.

immature leucocytes rose from between 0.5 and 4.0 in 1931 to between 13.5 and 19.5 in 1935, and have dropped slightly since then.

The non-leukaemic blood picture is not due to X-ray treatment in any of these cases.

The long course and the absence of much interference with the patient's general health are striking features. As a contrast to this Emile-Weil and Clerc (16) speak of rapid progress in their cases.

Spontaneous haemorrhages have occurred in all except Case 2. It is probable that these are more common in cases of non-leukaemic myelosis than in leukaemic cases. Many workers have commented upon this liability to spontaneous haemorrhage; for example, Émile-Weil and Clerc (16) and Hirschfeld (34).

The indirect van den Bergh reaction of the blood has given values constantly above normal limits in Cases 1, 3, 5, and 6. Not much information has been obtained from the literature with regard to the result of this test, as in the majority of cases it has not been carried out. Vaughan (69) and (70) found the result within normal limits in her cases of myelosclerosis and leuco-erythroblastic anaemia; Ballin and Morse (3) found the indirect van den Bergh reaction negative in one of their two cases; McMichael and McNee (46) found it positive in one of their cases. Some authors comment upon a yellowish colour which the patients present, for example, Roch and Mozer (60) and Hirschfeld (35); the latter says this yellowish colour is seldom missing.

In Cases 1, 3, and 6 persistently high blood uric acid values were found during the time that this estimation has been carried out. In Case 3 this was associated with very severe gouty arthritis. In the other two cases no gouty changes have so far appeared, though the values have been found to be more than double the maximum normal value of 4 mg. per 100 c.c. This finding should be correlated with metabolic studies; but the finding is sufficiently striking to be worthy of mention, and is in all probability of important significance. The literature gives very little information with regard to this matter. As far as leukaemic myelosis is concerned, Naegeli (50) states that the blood uric acid may be raised or may be normal; Vogel (73) found the average in 14 cases of leukaemia to be 4.2 mg. per 100 c.c., with a maximum of 6.9 and a minimum of 1.8; seven of the 14 had values of values of 5 mg. or more at some period. Folin and Denis (23) in two cases of myeloid leukaemia found values of 3.1, 2.8, and 4.1 mg. per 100 c.c. Gout may occur in patients with leukaemia under X-ray treatment; but the writer has not found any references to blood uric acid estimations in such cases.

In non-leukaemic cases Szilárd (67) found values varying from 6.2 to 8.9 in one case, and varying from 6.1 to 9.1 in a second. He attaches no importance to this finding, simply stating that these values show that there is no difference in this respect between leukaemic and aleukaemic cases of myelosis. Hagedorn (29) in a case of aleukaemic myelosis with osteo-

sclerosis found blood uric acid values of 10, 9.5, and 8 mg. per 100 c.c., but his patient had had gout in attacks for thirty years before he came under observation.

X-ray pictures of the skeleton in Cases 1 and 2 show the presence of well-marked 'osteosclerosis' (Plate 8, Figs. 1 to 4). There is a great increase in the number and thickness of the bony trabeculae traversing the medullae of the humeri, femor, and ribs. The parts of the pelvis and scapulae adjacent to the articulations with the femora and humeri are also affected. In Case 2 the same changes are also present in the clavicles and the upper parts of the tibiae. No changes in the skull or vertebrae can be made out in either case. Pictures of dried bones showing this great increase in the bony trabeculae are shown by Pastore (56) and Jores (39).

There are differences of opinion as to the significance of these bone changes. Naegeli (49) thinks that most of the cases in which they occur are not really cases of myelosis, but examples of extra-medullary blood formation secondary to the bony replacement of the bone-marrow cavities. Hirschfeld (34 and 35) regards the bone changes as an occasional accompaniment of aleukaemic myelosis, and is doubtful of their significance. These cases have been variously described as leukaemia with osteosclerosis, Schwarz (63), leukanaemia with increase in connective tissue in the bone-marrow, Parkes Weber (74), osteosclerotic anaemia, Assmann (2), Mozer (48), Chapman (11). There is a fibrosis of the bone-marrow or more characteristically an encroachment upon the bone-marrow cavities by new-formed bony processes. In most cases the part of the bone-marrow not affected by these changes has been found to be hyperplastic.

In the majority of cases in which osteosclerosis has been found, the most striking feature has been massive splenomegaly due to myeloid metaplasia, with immature red and white cells in the circulating blood, without a great increase in the total number of leucocytes. That is to say, most cases present the features of chronic non-leukaemic myelosis in the sense used in this paper.

In other cases considerable variation in the clinical course and blood picture has been found. Most cases have been chronic, but some have been acute, death occurring within a few months of the first symptoms. Such cases are recorded by Assmann (2) and Mozer (48). According to Hirschfeld (34) osteosclerosis has been occasionally observed in patients with a leukaemic blood picture, and Heuck (30) recorded such a case, the total leucocytes being 400,500 per c.mm. at first, falling to 80,000 and rising again to 169,000. In some cases with osteosclerosis the blood picture has been that of aplastic anaemia, and no myeloid metaplasia of the spleen and other organs has been found. Schmidt (62) and Mozer (48) each describe such a case. Reviews of osteosclerosis have recently appeared by Mozer (48), Chapman (11), and Vaughan (70).

It is not possible at present to know how frequently osteosclerosis occurs in cases of leukaemic myelosis and of non-leukaemic myelosis, for X-ray

investigations of the skeleton in these cases have not frequently been recorded. Changes in the bone-marrow of a fibrotic character could only be detected by complete post-mortem examination of the skeleton.

It is a striking fact that patients with massive myeloid splenomegaly and osteosclerosis show the same variations in the duration of the disease and in the type of blood picture as do cases of myeloid splenomegaly without osteosclerosis. In both groups there are acute and chronic cases; in both groups immature cells are usually present in the circulating blood, though rarely they may not be found; in both groups the blood may be 'leukaemic', that is to say, there may be a great increase in the number of circulating leucocytes, a high proportion of which are immature.

There appear to be no clinical or haematological features which would enable the presence of osteosclerosis to be diagnosed; this can only be done by X-ray examinations of the skeleton, or by post-mortem examination. It appears to the writer that the importance of the recognition of osteosclerosis lies in the light which a study of the cases may throw upon the problem of myeloid metaplasia, and of leukaemic myelosis, and that there does not appear to be, at present, sufficient reason for separating the cases of osteosclerosis with massive myeloid splenomegaly from cases of leukaemic and non-leukaemic myelosis.

Histological Observations

Case 2. The spleniculus removed at operation shows a normal appearance of the Malpighian bodies; the pulp is packed with cells, most of which are recognizable as myeloid cells, neutrophile, and eosinophile myelocytes, and nucleated red cells. Some hypertrophy of the endothelial cells is present, but not to a striking degree, and no histological evidence of phagocytosis is present. The appearance is that of myeloid metaplasia of the pulp, without involvement of the Malpighian bodies.

Case 4. The post-mortem examination had to be confined to the abdomen. There is myeloid metaplasia of the spleen, with disappearance of the Malpighian bodies; myeloid tissue is present between the columns of liver cells; there are small areas of myeloid infiltration in the kidneys; and in the raised areas of the skin, which developed in the two or three weeks preceding death, there is a striking infiltration with myeloid cells. In the abdominal lymph glands, which were found enlarged at the post-mortem examination, the normal structure is preserved, but in places there is an accumulation of myeloid cells. The examination of the bone-marrow had to be confined to that present in the bodies of the lumbar vertebrae. This shows that the fat spaces are preserved, and no obvious increased activity is manifest. Apart from the unsatisfactory examination of the bone-marrow, the histological picture is that of myelosis, with 'leukaemic' infiltration of the lower layers of the skin, in patches.

Case 3. The histological examination reveals intense myeloid metaplasia of the spleen, with disappearance of the Malpighian bodies; myeloid metaplasia of the liver; no changes in the kidneys; and an intensely active bone-marrow at the lower end of the right femur, which was the only part of the

skeleton examined. The most striking feature of the myeloid metaplasia is the presence of great numbers of giant cells, in the spleen, liver, and bone-marrow (Plate 9, Figs. 1 to 3). Most of these have the appearance of enlarged bone-marrow giant cells. In the liver they lie in vascular channels between the columns of liver cells, and sometimes appear to stretch across these vascular channels like diagrammatic Kupffer cells. Very little histological evidence of phagocytosis can be found, and no iron can be demonstrated by histological methods.

Giant cells of such size and in such numbers as to form the most striking feature of myeloid metaplasia have been described in a number of cases which I would include under the title non-leukaemic myelosis.

Schwarz in 1901 (63) described a case with osteosclerosis, myeloid metaplasia of the spleen, liver, and kidneys, with 'giant cell emboli' as a striking feature. The blood contained 23,000 to 40,000 leucocytes per c.mm., 18 to 22.5 per cent. of which were myelocytes, with numerous nucleated red cells. Michaelis, also in 1901 (47), described a similar case, without bone changes, with 'giant cell degeneration' of the blood-forming organs, this change being present in bone-marrow, spleen, liver, and lymph gland.

In the following papers, published since 1901, giant cells are described as forming a very striking feature of the histological picture:—

Hirschfeld and Alexander (36), Rathery (59), Askanazy (1), Hirschfeld (31), Nauwerck and Moritz (51), Bushnell and Hall (8), Assmann (2), Donhauser (13), Levy (42), Bianchi (7), Firket and Campos (22), Firket (21), Goldschmid and Isaac (27), Di Guglielmo (12), Barth (5), Fiessinger and Olivier (20), Körner (40), Ballin and Morse (3), Jaffé (38), Zadek (75), Dubinskaja (15), Speroni and Llambias (65), Gaudier and Houcke (26), Houcke (37), Downey, Palmer, and Powell (14), Favre, Croizat and Guichard (19), Carnot, Caroli, and Busson (9).

In all the cases described in these papers the giant cells have been present in association with myeloid metaplasia of the spleen, liver, and sometimes of the lymph glands. The bone-marrow has also contained very numerous giant cells, in association with hyperplasia. In six (1, 2, 13, 51, 63, 75) osteosclerosis has been present, in addition to the myeloid metaplasia with great numbers of giant cells. Many of the papers contain good pictures of the giant cells, for example, Bianchi (7), Barth (5), Dubinskaja (15). In none of the cases was the blood picture leukaemic; in all in which there is good evidence that careful blood examinations were carried out, young white or red cells, or both were present in the circulating blood. Most of the cases were chronic; but some were acute, death occurring within a few months of the onset of symptoms, for example, those of Hirschfeld and Alexander (36), Assmann (2), Donhauser (13), Firket and Campos (22). There has been considerable difference of opinion regarding the nature and origin of the giant cells. Most of the authors call them megakaryocytes or bone-marrow giant cells. Goldschmid and Isaac (27) describe a case with very minute details. They consider that the giant cells are of endothelial

origin; but that it is possible that megakaryocytes are derived from these Di Guglielmo (12) considers them to be true megakaryocytes, and that the megakaryopoietic system is particularly active in aleukaemic myelosis. Barth (5) thinks that the giant cells in his case were not megakaryocytes, but were of endothelial origin, and that the endothelial hyperplasia goes hand in hand with the leukaemic process (his case was not leukaemic, the total leucocytes never exceeding 36,200, the percentage of immature cells being about 30). Gaudier and Houcke (26) found intermediate stages between endothelial cells and megakaryocytes; and Houcke (37) in a study of the spleen from the last case states that the giant cells are acting as macrophages, but are also forming platelets. Favre, Croizat, and Guichard (19) think that there are transitions from reticulo-endothelial cells to megakaryocytes.

Comments

It appears that in some patients presenting the clinical picture of leukaemic myelosis (myeloid leukaemia), without a characteristic leukaemic blood picture, with myeloid metaplasia of some or all of the organs affected by this change in typical leukaemic myelosis, there occur certain features which either do not occur in, or are much less common in, leukaemic myelosis. These are sclerotic changes in the bone-marrow, with new bone formation in the marrow cavities of the bones; and the presence of giant cells in association with the myeloid metaplasia, of such size and in such numbers as to form its most striking feature. These two features have been found together in some cases; in others either one or the other has been found; and in others neither has been demonstrated. No information is available as to whether the bone changes precede or follow the changes in the organs and blood, or whether both develop together. My Case 1, who has been observed for thirteen years, unfortunately never had the skeleton investigated by X-rays until 1936.

It is suggested in addition that a high bilirubin content of the blood, and a high blood uric acid value are more common in the cases here considered than they are in cases of leukaemic myelosis. These two features seem to suggest an increased destruction of blood cells; this might be a compensatory process in a case which might otherwise present a leukaemic blood picture; or it is possible that the increased blood-cell destruction might be the primary process, and the myeloid metaplasia with increased size of the spleen and liver a manifestation of extra-medullary blood formation in an attempt to compensate for the increased destruction. The significance of these various features should become clear when numbers of cases have been thoroughly investigated from an early stage in the disease, and observed over a long period of time. No doubt there are other special features which further investigation will reveal; a study of these cases of non-leukaemic myelosis may throw light upon the problem of the nature of myelosis.

No attempt is made to discuss similar changes that occur in infants and children, for example, Albers-Schönberg's disease, and von Jaksch's anaemia, though it is probable that they are related to the adult cases discussed here.

Summary

1. An account is given of some cases presenting the clinical features of leukaemic myelosis (myeloid leukaemia), with some or all of the histological changes of that disease, but without the characteristic blood picture.

2. It is doubtful whether this condition occurs without there being immature cells in the blood, but careful and repeated examinations may be needed to find them.

3. The danger of surgical interference with the spleen is emphasized by cases collected from the literature, and by its effect upon one case in the present series.

4. There are certain features which are more common in these cases than in typical cases of leukaemic myelosis, among which are abnormal bone formation in the bone-marrow cavities; and the presence of large numbers of giant cells in the myeloid tissue of the organs.

Acknowledgements

Dr. Patterson, Chemical Pathologist to Charing Cross Hospital, carried out the uric acid estimations and van den Bergh reactions. Dr. Gordon Holmes, Dr. Shirley Smith, and Mr. Cameron MacLeod allowed me to take over for investigation Cases 3, 5, and 6 respectively. Dr. A. E. Russell allowed me to make use of his notes upon Case 1, made during the years 1923 to 1926. Dr. Coldwell took the X-ray pictures of Case 2 and supplied me with pictures of normal bones for comparison. I am most grateful to all these gentlemen for their kind help.

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FIG. 1. X-ray of humerus of Case 2, showing osteosclerosis



FIG. 2. X-ray of a normal humerus, for comparison



FIG. 3. X-ray of femur of Case 2, showing osteosclerosis



FIG. 4. X-ray of a normal femur, for comparison

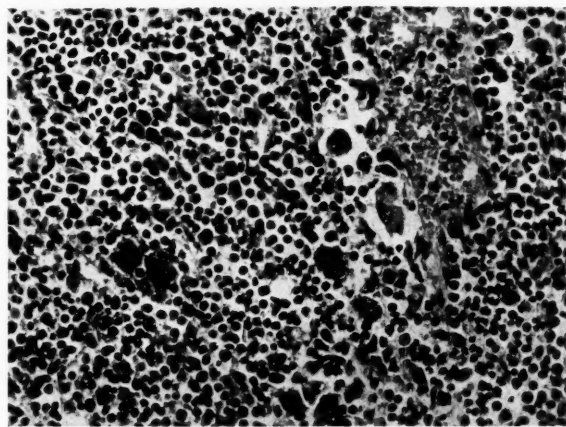


FIG. 1. Section of hyperplastic bone-marrow from the lower end of the femur of Case 3, showing presence of numerous giant cells

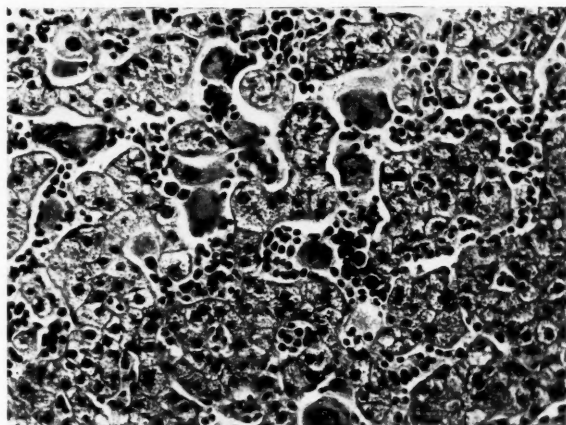


FIG. 2. Section of liver, from portion removed at operation, of Case 3, showing giant cells and myeloid tissue between the columns of liver cells

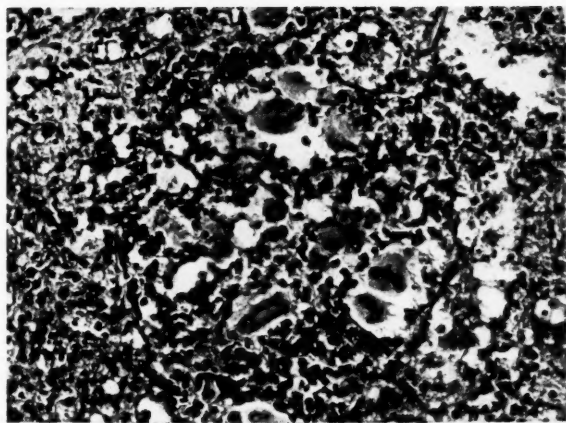
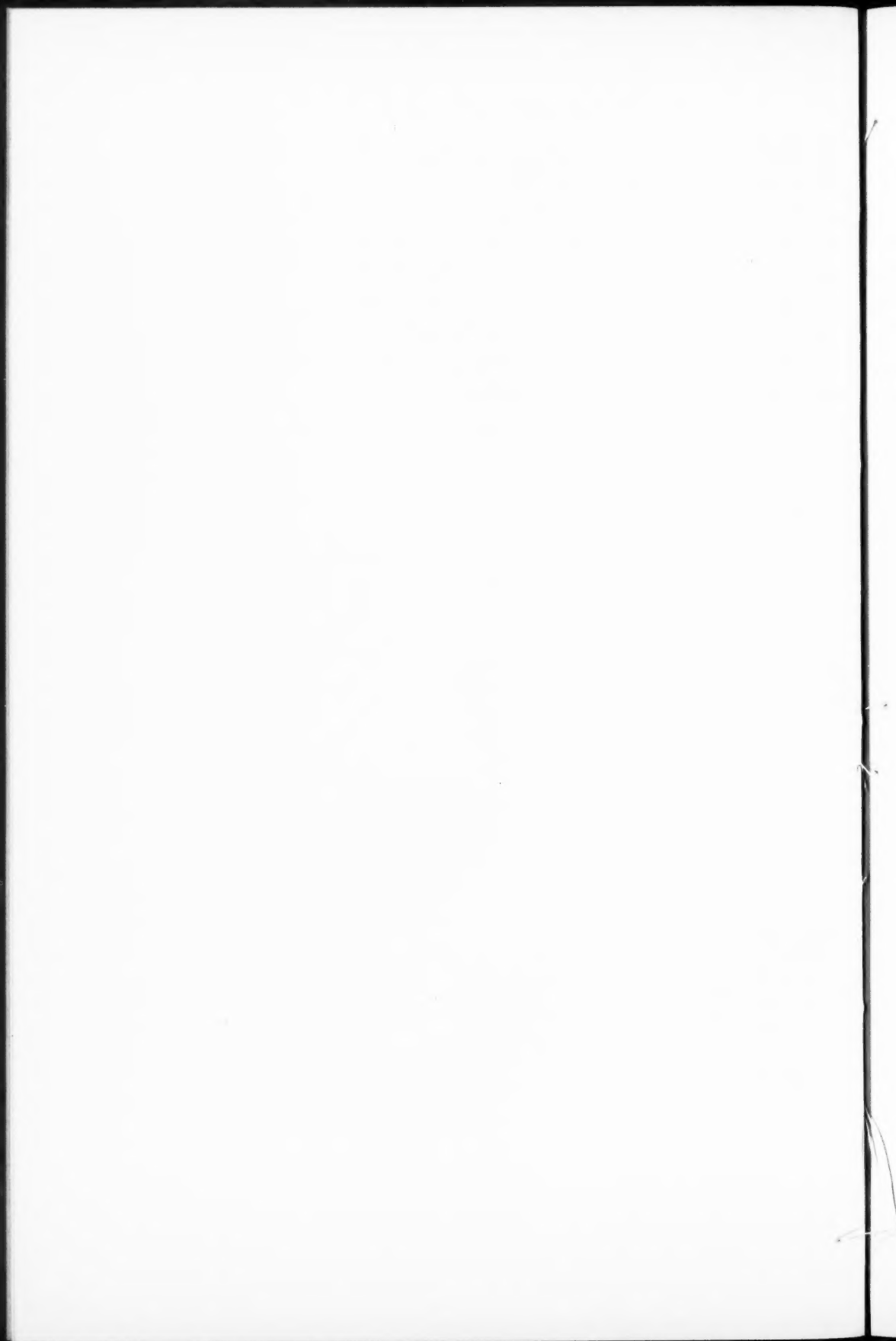


FIG. 3. Section of spleen, from portion removed at operation, of Case 3, showing myeloid metaplasia, with large numbers of giant cells

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THE FATE OF THE ELEMENTS REMOVED FROM THE BLOOD-STREAM DURING THE TREATMENT OF POLYCYTHAEMIA BY ACETYL-PHENYLHYDRAZINE¹

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Introduction

A GREAT deal of work has been done on the metabolism of iron in the past few years, and the majority of this work has consisted in the administration of iron or some stimulant of red-cell formation and in following the effects of this by a study of the rate at which red-blood corpuscles appear in the circulation. It is often not realized that the red-blood cells contain, not only iron, but also large amounts of nitrogen and potassium. These have seldom been studied during the active phases of blood regeneration. In many ways active blood destruction is a more suitable subject for metabolic study than blood formation, since the former process is extremely rapid and can be reproduced experimentally both in humans and animals in a number of different ways. Studies have been made of iron metabolism during the treatment of polycythaemia vera (Bassett, Killip, and McCann (1); Reznikoff, Toscani, and Fullarton (21)). These authors agree that during an extensive destruction of red cells, which led to a disappearance of 2,000–3,000 mg. of iron from the blood-stream, negligible quantities only of this iron were excreted. The full significance of these findings does not seem to have been generally appreciated. It is evident from the literature that a rise of blood urea may accompany treatment of polycythaemia with phenylhydrazine (Harrop (3)), and although this has been attributed to some toxic effect of the drug upon the kidneys, it is clear that a rise of blood urea should be expected if forced metabolism of some hundreds of grammes of nitrogen takes place when the red-blood cells are destroyed. Bassett, Killip, and McCann (1) stated that they expected from the haemoglobin destruction a negative balance of 198 grm. nitrogen, but they obtained a negative nitrogen balance of only 134 grm. during the period of active blood destruction. They concluded that some nitrogenous portions of the disintegrated red cells must have been retained, possibly to be re-utilized in the formation of new haemoglobin. Actually, their figures do not quite bear out this statement. Approximately 870 grm. of haemoglobin were destroyed. If this contains 16.9 per cent. of nitrogen (Oldfeldt (19)), the nitrogen set

¹ Received February 20, 1937.

free is 146 grm., not 198 grm. Their balance experiment, moreover, was rather unsatisfactory in that there was a negative balance throughout the whole experiment, not only during the period of blood destruction, so that their total negative nitrogen balance was 156 grm. It is doubtful, therefore, whether their conclusions were fully justified.

Huffman (11) investigated the nitrogen metabolism of four polycythaemic patients during treatment with phenylhydrazine. He found in each case a large negative nitrogen balance, but merely stated that the estimated destruction of blood was more than sufficient to account for the negative balance. An examination of his figures shows that not only was this true, but that in actual fact he sometimes accounted for only a fraction of the nitrogen set free on the basis of haemoglobin destruction. Thus, in Case 3, 530 grm. of nitrogen were set free, but the negative balance only amounted to 175 grm. It is true that the faeces were not considered, but no serious error would have been introduced by this omission.

No potassium balances seem to have been made during a time of active blood destruction, and accordingly it was decided to make a metabolic study of the nitrogen, iron, and potassium when a case suitable for treatment with phenylhydrazine presented itself.

Clinical Notes on the Patient

Mrs. H., aged 61. Weight 40 kg. (6 stone). Admitted to King's College Hospital on 22nd September, 1936. Her blood count on admission was 10·91 million, and her haemoglobin was 163 per cent. (Haldane). Colour index 0·75. Physical and radiological examination failed to reveal any pulmonary or circulatory cause for the polycythaemia, and a diagnosis of polycythaemia rubra vera was accordingly made. Clinically the patient was relatively symptom free. Her blood-pressure was 120/70. She was, however, very conscious of her unusual appearance, and reported that slight haemorrhages were very difficult to control. There was no evidence of any intestinal ulceration, and the stools gave negative tests with benzydine. It was decided to treat the patient with acetyl-phenylhydrazine (Stone, Harris, and Bodansky (23)). The drug appeared to have no toxic effects. The patient lost her appetite for a few days after the phenylhydrazine had been stopped, at the time when her haemoglobin level was falling most rapidly, but this can hardly have been due to the drug itself. She also had a slight rise of temperature at this time, and was kept in bed for a few days. Oedema could be detected over both ankles and in the lumbar region when her haemoglobin was at its lowest levels. Otherwise, treatment was marked by no untoward symptoms or complications.

Metabolic Technique

Urine and faeces, and duplicate portions of all foods, drinks, and medicines were collected in three-day periods and set aside for analysis. They were treated in the following way.

Food. Bread and biscuits were dried in the oven at 100° C. for several hours, ground to a powder, and mixed with the remainder of the food. The whole was then weighed and portions were taken for analysis.

Fluids. All beverages, including water and tea, were collected in three-day periods, mixed, measured, and sampled for analysis. For technical reasons they were analysed separately from the solid food.

Urine. The urine was passed into porcelain vessels and stored in glass bottles under toluene. Half of the urine passed in each twenty-four hours was set aside to form part of the collection for the three-day period. A further portion of about 300 c.c. was stored separately for urea estimation.

Faeces. These were passed into porcelain vessels, and carmine was given by mouth at the beginning of each three-day period. The combined stools for three days were weighed and portions were tested with benzidine. The remainder was mixed thoroughly with A.R. glacial acetic acid, dried at 50° C. overnight and for a further twenty-four hours at 100° C. It was then weighed, ground to a fine powder, and stored for analysis.

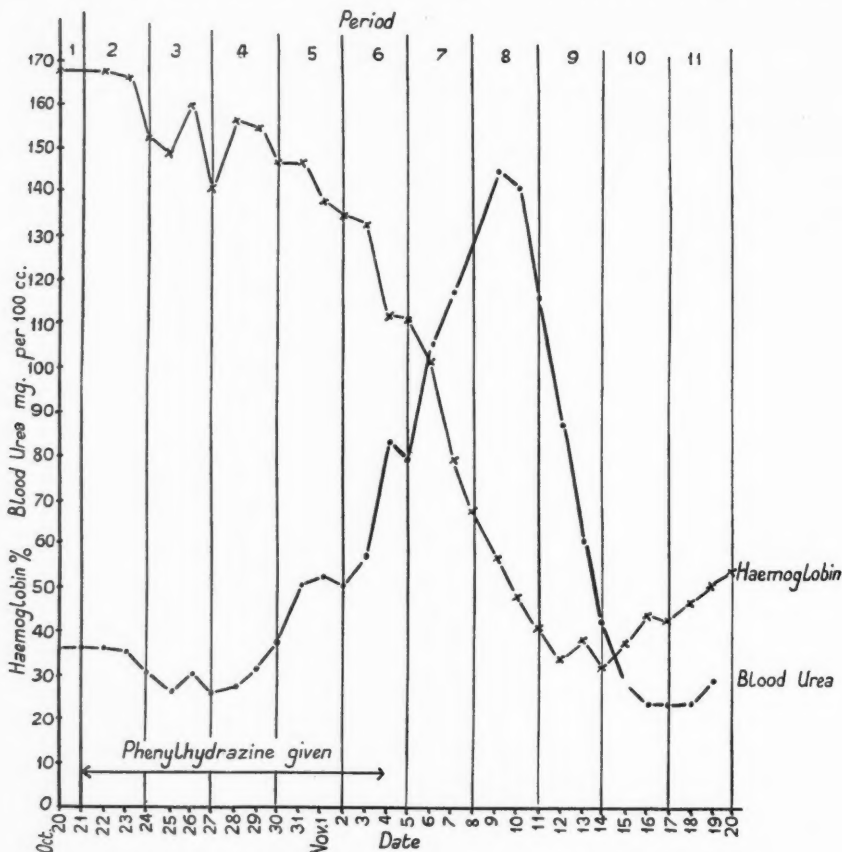
Methods

1. *Urine.* Total nitrogen. Kjeldahl. McCance and Shipp (13).
McCance, Widdowson, and Shackleton (16).
Urea. Modification of the Beattie (3) procedure.
Creatinine and creatine. Folin. Hawk (10).
Ammonia. Conway (7).
Potassium } After incineration.
Iron } McCance and Shipp (13).
Copper } McCance, Widdowson, and Shackleton (16).
2. *Faeces.* Total nitrogen, potassium, iron, and copper as for urine.
3. *Whole Blood.* Total nitrogen, urea, potassium, iron, and copper as for urine.
Cell-volume. Haematocrit. Blood collected under paraffin without constriction. Coagulation prevented by heparin.
Haemoglobin. Haldane. 100 per cent. = 13.8 gm. Hb. per 100 c.c.
Cell counts. Thoma counting chamber.
4. *Plasma.* Copper as for urine.
Proteins. Kjeldahl. McCance and Watchorn (14).
5. *General.* Blood-volume. Keith, Rowntree, and Geraghty (from Peters and Van Slyke (20)).

Treatment and Experimental Procedure

The patient was placed on a diet containing about 7 gm. of nitrogen, 2 gm. of potassium, 3-4 mg. of iron, and 0.5 mg. of copper per day. The first three days were treated as introductory. Collections were made, but no analyses were carried out. The second three days (period 1) served as a control. Quantitative collections were made, but no acetyl-phenylhydrazine was given. During this time blood was taken by vein puncture for analysis and the patient's blood-volume was determined.

Acetyl-phenylhydrazine was given from the commencement of the next three-day period (period 2) in doses of 0.3 gm. a day. (Total amount given 4.2 gm.) This treatment was continued until the patient's haemoglobin had fallen from the original 168 to 110 per cent. Determinations of haemoglobin and blood urea were made every day. The effect of treatment on the haemoglobin and blood urea are shown graphically in the chart. The haemoglobin curve shows the usual response to medication of this sort.



The greatest fall occurred after the drug had been discontinued, and at the time of this most rapid destruction of red cells the blood urea reached the high figure of 145 mg. per 100 c.c.

Other observations made at this time are given under 'Clinical Notes'.

The patient's urea clearances, as calculated from the twenty-four hour urines are given in Table I. They were generally below the accepted standards of normality even when the small size of the patient was taken into account. Kidney failure due to the action of the drug, however, was evidently not the cause of the rise in the blood urea for there was no fall in clearance while acetyl-phenylhydrazine was being given, or until the blood urea had risen to 106 mg. per 100 c.c.

TABLE I

Urea Clearances on 24-hour Urines. For Blood Ureas see Figure 1

Date.	Minute volume.	% Urea in urine.	Clearance %. Van Slyke formula. Corrected for surface area.	Date.	Minute volume.	% Urea in urine.	Clearance %. Van Slyke formula. Corrected for surface area.
	c.c.				c.c.		
Oct. 21	0.50	1.77	76	Nov. 6	0.89	2.71	52
" 22	0.51	1.60	68	" 7	1.08	2.08	40
" 23	0.49	1.47	63	" 8	0.98	2.56	41
" 24	0.59	1.10	63	" 9	0.99	2.38	35
" 25	0.58	1.25	77	" 10	0.92	2.16	32
" 26	0.62	1.11	63	" 11	0.90	1.97	35
" 27	0.95	0.72	58	" 12	0.66	2.08	42
" 28	0.90	1.21	91	" 13	0.52	1.97	50
" 29	0.60	1.48	78	" 14	0.58	1.57	60
" 30	0.58	2.00	88	" 15	0.55	1.16	65
" 31	0.76	2.02	75	" 16	0.79	0.67	54
Nov. 1	0.68	2.02	68	" 17	0.84	0.65	53
" 2	0.79	2.02	76	" 18	0.90	0.69	57
" 3	0.59	3.16	91	" 19	0.93	0.64	45
" 4	0.63	3.05	63				
" 5	0.76	2.87	68				

TABLE II

	Before treatment 20.10.36.	After treatment 18.11.36.
Haemoglobin %	168	47
R.B.C. (millions per c.mm.)	10.82	2.35
Colour index	0.78	1.0
Cell volume %	87	25.5
Mean corpuscular volume (μ^3)	80	108
Blood volume (c.c.)	8,460	3,820
Plasma volume (c.c.)	1,268	2,850
Iron in blood (mg. per 100 c.c.)	85	22.4
" " Total mg.	7,190	856
Potassium in blood (mg. per 100 c.c.)	432	132
" " Total mg.	36,500	5,000
Total nitrogen in blood (gm. per 100 c.c.)	4.53	1.69
" " " Total g.	384	65
Copper in blood (mg. per 100 c.c.)	0.21	0.30
" " " Total mg.	17.8	11.4
Copper in plasma (mg. per 100 c.c.)	0.19	0.32
Proteins in plasma (gm. per 100 c.c.)	4.42	4.96

Results

The changes in the blood. The patient's blood before the phenylhydrazine was given had a volume of 8,460 c.c. i.e. 216 c.c. per kg. It contained 384 gm. of nitrogen, 7.19 gm. of iron, 36.5 gm. of potassium, and 17.8 mg. of copper. At the end the blood had a volume of 3,820 c.c. and it contained 65 gm. of nitrogen, 0.86 gm. of iron, 5.0 gm. of potassium, and 11.4 mg. of copper. For further details see Table II. During the course of the treatment, therefore, 319 gm. of nitrogen, 6.33 gm. of iron, 31.5 gm. of potassium, and 6.4 mg. of copper were set free inside the body. The colour index of the

TABLE III
Metabolic Balances

Period.	Iron (mg.)			Potassium (gm.)			Nitrogen (gm.)			Copper (mg.)		
	Intake.	Output.		Intake.	Output.		Intake.	Output.		Intake.	Output.	
		Urine.	Faeces.		Urine.	Faeces.		Urine.	Faeces.		Urine.	Faeces.
		Total.			Total.			Total.			Total.	
1	11.3	0.8	8.2	9.0	6.85	4.12	0.83	4.95	22.6	20.3	2.1	22.4
2	11.9	0.6	10.0	10.6	7.03	4.45	1.31	5.76	30.9	19.7	2.7	22.4
3	10.5	0.7	15.8*	16.5*	5.88	3.52	0.76	4.28	22.3	17.0	2.1	19.1
4	10.0	0.7	16.6	17.3	6.38	4.77	1.33	6.10	26.7	22.9	3.1	26.0
5	11.1	0.8	9.4	10.2	5.89	5.30	0.82	6.12	24.2	31.4	2.3	33.7
6	15.7	4.5	8.9	13.4	6.99	6.77	1.08	7.85	26.8	42.5	2.3	44.8
7	8.0	14.6†	12.4	27.0†	4.55	7.60	1.76	9.36	15.3	59.5	2.8	62.3
8	14.4	3.0	14.7	17.7	5.64	6.10	1.07	7.17	16.6	55.6	3.8	59.4
9	17.3	2.2	14.6	16.8	4.61	4.00	0.50	4.50	18.5	32.0	1.9	33.9
10	15.3	2.2	14.8	17.0	4.75	3.84	0.58	4.42	17.2	17.0	2.5	19.5
11	18.4	2.8	14.0	16.8	4.75	3.68	0.58	4.26	20.8	14.0	1.8	15.8
Total	143.9			172.3	63.32			64.77	241.9			359.3
Balance											-1.45 gm.	
											-117.4 gm.	
											-2.26 mg.	

* The mixed faeces for this three-day period gave a strongly positive benzidine reaction.

† The mixed urine for this three-day period gave a positive benzidine reaction.

blood was 0.75 when treatment was commenced and the mean corpuscular volume was $80 \mu^3$. After treatment the colour index had risen to 1.0 and the mean corpuscular volume to $108 \mu^3$. Thus the new cells were larger than the old ones and contained more iron. This suggests that the patient was relatively iron-deficient, and remained so until sufficient iron had been set free to enable her to manufacture red cells containing normal quantities of haemoglobin.

The metabolic balances. The results of the balance studies are shown in Table III.

It is to be noted—

1. That the intake and output of iron may be considered almost to balance. Actually there was a negative balance of 28 mg. throughout the whole period. This is negligible when compared with the amount of iron (6,330 mg.) removed from the blood by the phenylhydrazine.

The greatly increased urinary output of iron during period 7 was due to haemoglobin, for the urine at this time gave a strongly positive benzidine reaction. Similar results have been obtained by others working with haemolytic agents (Muir and Dunn (17, 18), Dubin and Pearce (8), Huffman (11), Bassett, Killip, and McCann (1)). No other urines gave positive tests with benzidine. The increased urinary excretion of iron in periods 8–11 must therefore have been due to a greater excretion of inorganic iron. This strongly suggests that the renal excretion of iron can vary within narrow limits under certain conditions.

2. That the negative balance of nitrogen amounted to 115 gm. Large though this may appear to be, it was only one-third of the amount set free by the break-down of red cells. The remainder must have remained inside the body.

3. That the negative balance of potassium (1.45 gm.) represented only 5 per cent. of the total amount liberated.

4. That the negative balance of copper was 2.26 mg. During the period of blood destruction 6.4 mg. were set free, so that about 30 per cent. of this was excreted.

Discussion of the balance experiments. The failure of the body to excrete the iron during the destruction of the red-blood cells fully confirms the results of Bassett, Killip, and McCann (1) and of Reznikoff, Toscani, and Fullarton (21). Indeed, this result in some form or another has been obtained by numerous observers (Muir and Dunn (17), Dubin and Pearce (8), Brugsch and Irger (5)), and there can be no doubt of its general truth. The body, then, does not excrete iron under these conditions.

To explain this fact by invoking the magnificent storage capacity of the body is merely to blind oneself to the obvious suggestion that the body is incapable, under these conditions, of excreting iron which is wholly unnecessary for its present well-being. This raises most interesting issues as to the capacity of the body to excrete iron at any time. This will be made the subject of a separate communication (McCance and Widdowson (15)).

The failure to account for more than one-third of the nitrogen set free from the blood is a more original observation, although Huffman (11) appears to have made it without appreciating its significance. The magnitude of the 'loss' is demonstrated by the fact that 200 grm. of nitrogen, which was the amount set free but not excreted, are equivalent to about 10 lb. of hydrated body tissues. If 200 grm. of nitrogen in the form of globin had been taken by mouth over this period, there is little doubt that all or practically all of it would have been excreted in the urine. The fact that only one-third of the protein leaving the blood was excreted suggests that the remainder was not catabolized to amino acids. Where was it stored, and in what form? The answers to these questions are at present uncertain, but the spleen and liver are likely storage sites, and Samuely (22), Underhill (25), and Bodansky (4) observed considerable splenic and hepatic enlargement in animals which had been rendered anaemic by phenylhydrazine.

It is not unreasonable to suppose that globin itself was the protein stored, for it has been suggested that globin set free on the destruction of red-blood cells may be directly utilized again in the formation of new ones (Taylor et al (24), Knutti et al (12), Castle and Minot (6)).

These problems are undergoing further investigation. The failure to account for 95 per cent. of the potassium which left the blood-stream is not altogether surprising in the light of the nitrogen retention. If the nitrogen was retained as protein within cellular structures, then there is good reason to suppose that potassium salts would have been retained with it to maintain the intra-cellular osmotic pressure of the body within normal limits.

The copper balance is much less spectacular than that of the other three elements. If any conclusions may be drawn from an isolated metabolic experiment on an element present in such small traces in the food and excreta, the results suggest that the body has more capacity to excrete copper than iron, and that it does so through the medium of the kidney. The fluctuations in the excretion of copper in the urine represent a significant proportion of the total turnover, and the rise in the excretion rates coincided with the periods of active blood destruction. The excretion in the faeces was irregular, which suggests that the intestine was not playing a part in regulating the copper level of the body.

The partition of nitrogen in the urine. The results are given in Table IV, and some interesting points emerge from their consideration. In the first place, the patient was excreting considerable amounts of creatine before the experiment began, and unusually little creatinine. This is probably due to extremely poor muscular development. Secondly, not only the urea, but also the undetermined nitrogen and the creatine-creatinine fraction contributed to the great increase of urine nitrogen excreted during the period of active blood destruction. While the creatinine excretion altered little, the creatine excretion rose from 0.43 grm. in three days to 1.11 grm., and fell again when the period of blood destruction was over. There is no

TABLE IV
Nitrogen Partition in Urines

Period.	Total N. gram.	Urea N. gram.	Ammonia N. gram.	Creatinine N. gram.	Creatine N. gram.	Undetermined N. gram.
1	20.3	18.2	0.54	0.62	0.43	0.51
2	19.7	16.3	0.52	0.56	0.54	1.78
3	17.0	13.8	0.49	0.57	0.49	1.65
4	22.9	18.0	0.54	0.64	0.64	3.08
5	31.4	26.4	0.77	0.67	0.69	2.87
6	42.5	36.4	1.04	0.72	0.81	4.53
7	59.5	48.5	1.37	0.77	1.11	8.75
8	55.6	46.2	2.00	0.84	0.78	5.78
9	32.0	26.8	2.30	0.76	0.49	1.65
10	17.0	14.3	1.22	0.73	0.28	0.47
11	14.0	11.8	0.82	0.72	0.29	0.37

reason to suppose that active destruction of muscular tissues was in progress during the destruction of the red-blood cells, and since the latter contain so little creatine, the creatine must have come from some other source. An increased excretion of creatine, when dogs were treated with phenylhydrazine, was observed by Underhill and Kleiner (26). Beard and Boggess (2) have found that if certain amino acids, notably arginine and histidine, are injected into rats, increased amounts of creatine are found in the muscles. Since globin contains large amounts of histidine it is possible that the forced metabolism of such quantities of this amino acid may have been the cause of the increased excretion of creatine. Thirdly, the ammonia nitrogen also rose and fell during the period of observation. The peak occurred in period 9, six days after the urea excretion had begun to fall, and at the time when the haemoglobin was at its lowest point and relatively constant. Fourthly, the excretion of urea accounted for 80-90 per cent. of the total nitrogen throughout the experiment.

Summary

1. Metabolic balances of iron, nitrogen, potassium, and copper have been carried out during treatment of a polycythaemic patient with acetyl-phenylhydrazine.

2. Less than 0.5 per cent. of the total amount of iron liberated by the destruction of red cells was excreted.

3. Only 30 per cent. of the nitrogen, 5 per cent. of the potassium, and 30 per cent. of the copper removed from the blood were excreted.

4. The most rapid blood destruction took place after the drug had been discontinued. At this time the blood urea rose to 145 mg./100 c.c. The urea clearance did not fall during the administration of the drug, but fell when the blood urea was at its highest levels. The blood urea subsequently returned to a low normal figure.

5. Increased excretion of urea, creatine, and undetermined nitrogen occurred during the period of active blood destruction.

The authors wish to thank all those who have assisted them at different stages of the investigation.

One of them (E. M. W.) is indebted to the Medical Research Council for a part-time grant.

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A QUANTITATIVE ESTIMATION OF THE PANCREATIC ISLET TISSUE¹

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THE questions considered in this investigation are :

1. What is the weight of islet tissue in a pancreas? Does this quantity increase after birth?
2. What is the number of islets in a pancreas? Do the islets increase in number after birth?
3. Do the islets increase in size after birth?
4. If, after birth, there is an increase in the weight of islet tissue and in the number and size of the islands what are the rates of increase of these factors relative to each other, to the weight of the body, and to the pancreatic acinar tissue? To what extent do these factors vary at the same age period?
5. Can the greater tolerance for sugar which obtains during the earliest years of life be explained by the presence in the infant pancreas of a quantity of islet tissue relatively greater than is found in the adult organ?

Material and Methods

The material consisted of 100 pancreases obtained from subjects (59 female and 41 male) varying between newly-born infants and an adult 64 years of age all of whom appeared *post mortem* to have been normally nourished. These subjects, it may be mentioned, died from a great variety of diseases, e.g. bronchopneumonia, cerebral haemorrhage, perforated gastric ulcer, burns, &c.

(1) *Estimation of weight of islet tissue.* The method devised was an extension of that described in a previous paper (Ogilvie (16)). Though then regarded as original it was later found to have been first described and used by Heiberg (8), but this investigator employed it to calculate the weight of islet tissue in only a single pancreas, and so far as can be found this is the only instance in which the actual weight of islet tissue has been determined.

Each pancreas was carefully dissected out, freed as much as possible from fat and weighed in grammes. Blocks of tissue were taken from the head, body, and tail of the organ and fixed in Helly's bichromate-sublimate-formalin

¹ Received March 15, 1937.

solution. Paraffin sections were prepared from these and stained by the azan method which was generally found to give a fairly good differentiation between islet and acinar tissue.

The stained section from the head of the pancreas was fixed into a microscope with the tube placed horizontally instead of vertically. With a strong carbon-arc light at the objective end (Watson para 2/3) and a prism fitted to the eye-piece (Watson 4) an image of the section with a magnification of 120 was cast on a sheet of quarto notepaper. By means of the movable stage fifteen unselected fields of the section were made to pass over this sheet of paper on which all the islands of Langerhans were traced in pencil. To estimate the total area of islet tissue in those fifteen fields the sheet was first weighed in grams and its area measured in square centimetres: then all the islands were cut out of the sheet with scissors and the weight of these were determined separately. Since

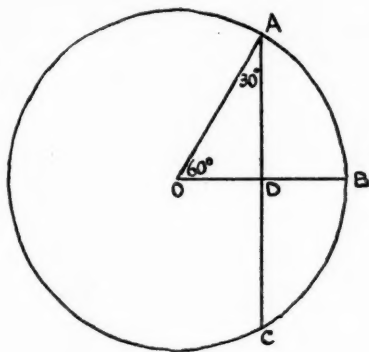
$$\frac{\text{area of islet tissue}}{\text{area of sheet}} : \frac{\text{weight of islet paper}}{\text{weight of sheet}}$$

it was possible to calculate the area of islet tissue contained in fifteen fields of pancreas. By direct measurement of the radius the area of one field was estimated and so the area of fifteen fields. In this way the percentage area of islet tissue in the head of the pancreas was obtained. The percentage area of islet tissue in the body and tail of the organ was estimated in the same way and an average was struck for the whole organ. This percentage figure was applied to the weight of the organ and so, on the supposition that islet and acinar tissue have the same specific gravity, the weight of islet tissue was finally calculated. In the case of infant pancreases, sections of which were too small to give fifteen fields, as many fields as possible were examined and the figure for fifteen fields was calculated therefrom.

The sources of possible error in this method were: (1) in infant pancreases it was sometimes difficult to distinguish islets from ductules and acini. This is understandable in view of the generally accepted origin of both acini and islets from ductules (Laguesse (11, 12); Pearce (18); Küster (9)), but with experience a fairly high degree of accuracy in differentiation was obtainable. (2) Only forty-five fields were examined in each pancreas, but the tediousness of the method did not allow of the examination of more. In order to cover regional differences the fields, it will have been noted, were distributed equally between head, body, and tail. (3) In calculating the weight of islet tissue from the percentage area it was taken for granted that islet and acinar tissue have the same specific gravity. There is naturally no way of proving this, but the difference, if any, is probably minimal.

2. *Estimation of total number of islets.* From the total area of a known number of islets in the head of the pancreas the average area of one islet on section was calculated. Similarly the average area of one islet in the body and in the tail was estimated and a final average was obtained for the whole organ. Now, if the average island be regarded as a sphere, $OABC$

(see sketch), then all sections of the average island must represent planes between the centre of the sphere, O , and its periphery B . Therefore, the average sectional area as calculated represents the area of a circle whose diameter, ADC , passes at right angles through the midpoint D , of OB , the radius of the average sphere. From the area of this circle its radius AD was calculated. OD being $\frac{1}{2} OA$ and $\angle ODA$ being 90° , $\angle OAD$ was 30° .



From the equation $\tan \angle OAD (30^\circ) = \frac{OD}{AD}$, the line OD was determined since it was the only unknown. $2OD$ gave OB , the radius of the average sphere. The real size of OB was obtained on division by 120, the power of magnification. From this radius the volume of the sphere $OABC$ ($\frac{4}{3}\pi r^3$) was calculated. Then taking into consideration the specific gravity of pancreatic tissue (found by separate experiment to be 1.05) and assuming as before that islet and acinar tissue have the same specific gravity, the weight of an average islet was estimated from the formula, mass = density \times volume. Knowing thus the weight of an average island and the total weight of islet tissue the total number of islets was calculable.

The method can be summarized thus:

Area of average island on section = $\pi r^2 = x$.

$$\therefore r = AD = \sqrt{\left(\frac{x}{\pi}\right)}.$$

$\therefore R$ = real radius of average islet (sphere $OABC$)

$$= \frac{AD \times 2 \tan 30^\circ}{120} = \frac{AD \times 2 \times .5774}{120} = .0096 AD$$

$$\begin{aligned} \therefore \text{Volume of average islet} &= \frac{4}{3} \pi (AD \times .0096)^3 \\ &= 4.1 (AD \times .0096)^3. \end{aligned}$$

$$\begin{aligned} \therefore \text{Mass of average islet} &= \text{Volume} \times \text{Density} \\ &= 4.1 (AD \times .0096)^3 \times 1.05. \end{aligned}$$

$$\therefore \text{Number of islets} = \frac{\text{Total weight of islet tissue}}{4.1 (AD \times .0096)^3 \times 1.05}.$$

The factors assessable in each case were thus: (1) Body-weight. (2) Weight

of pancreas. (3) Weight of acinar tissue. (4) Weight of islet tissue. (5) Weight of acinar and islet tissue per kilogramme body-weight. (6) Average weight of one islet. (7) Total number of islets of Langerhans.

The calculation of a case is demonstrated in Table I.

TABLE I

Sex and age.	Pan-creas.	No. of fields.	Wt. of sheet in grm.	Wt. of islands in grm.	Area of sheet in sq. cm.	Area of islands in sq. cm.	Area of pancreas in 15 fields in sq. cm.	Percentage area of islet tissue in pancreas.	No. of islands in 15 fields.		
Male	Head	15	4.60	1.68	516.64	188.7	4,996.8	3.77 } Average age	137		
2 yrs.	Body	15	4.59	1.09	516.64	122.7	4,996.8		132		
2 mths.	Tail	15	4.61	1.63	516.64	182.7	4,996.8		3.65 } 3.29	155	
Sex and age.	Pan-creas.	Average area of 1 island in sq. cm.	Wt. of pan-creas in grm.	Wt. of islet tissue in grm.	Wt. of acinar tissue in grm.	Body wt. in kg.	Wt. of islet tissue per kg. body wt. in grm.	Wt. of acinar tissue per kg. body wt. in grm.	Average wt. of one island. in γ	No. of islands.	
Male	Head	1.38	Aver- age	19.3	0.64	18.7	12.7	0.050	1.5	0.840	755,952
2 yrs.	Body	0.93									
2 mths.	Tail	1.18									

Results and Analysis of Investigation

Examination of 100 cases yielded figures summarized in Table II.

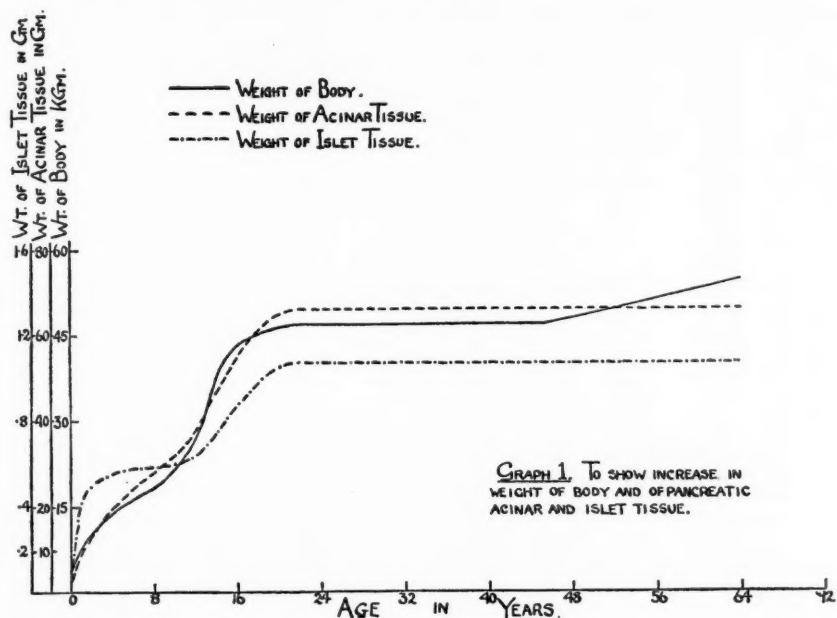
1. *Weight of (a) body; (b) acinar tissue; and (c) islet tissue.* The increase in weight of the body and of the acinar and islet tissue is shown in Graph 1 each curve of which was carefully constructed in a separate and detailed graph.

(a) It is seen that from an average at birth of 3.5 kg. the body-weight increases rapidly during the first two years of life, the increase being particularly marked during the first year. During childhood (4-12 years) the increase is less marked but steady, while adolescence (13-21 years) is characterized by another period of relatively rapid growth. About 21 years the body-weight becomes stabilized at an average of 48 kg. and there it remains until 45 years. After this age the weight shows an upward trend which can probably be explained by an increase of the fat in the depots. Of the 11 cases upon which this late increase is based five are female and six male.

(b) The acinar tissue of the pancreas exhibits a curve similar to that defining the increase in body-weight, except that the terminal rise is absent. It increases from an average of 2.6 grm. at birth to a stabilized figure of 66 grm. at 21 years. An observation which is lost in the composite graph but which is readily discernible in the detailed graph is the fact that the weight of acinar tissue at all ages between birth and 64 years varies within definitely wider limits than does the body-weight.

(c) The islet tissue increases from an average of 0.12 grm. at birth to

1.07 grm. at 21 years, and while this increase is similar to that of the body-weight and acinar tissue the curve shows that the increase of islet tissue is less marked during childhood than in the case of the other two factors. From the original graph, moreover, it is clear that from birth to 64 years of age the weight of islet tissue varies within wider limits than both the acinar tissue and body.



Further facts of interest are revealed by a consideration of the relative rates of increase of these three factors as shown in Table III and Graph 3. In this analysis the periods considered are the first, second, and third years of life, childhood (4-12 years), adolescence (13-21 years) and adult life (22-64 years). The figures tabulated were obtained from the curves in Graphs 1 and 2 and also by a careful consideration of the ratios $\frac{\text{weight of acinar tissue}}{\text{weight of body}}$, $\frac{\text{weight of islet tissue}}{\text{weight of body}}$, and $\frac{\text{weight of islet tissue}}{\text{weight of acinar tissue}}$.

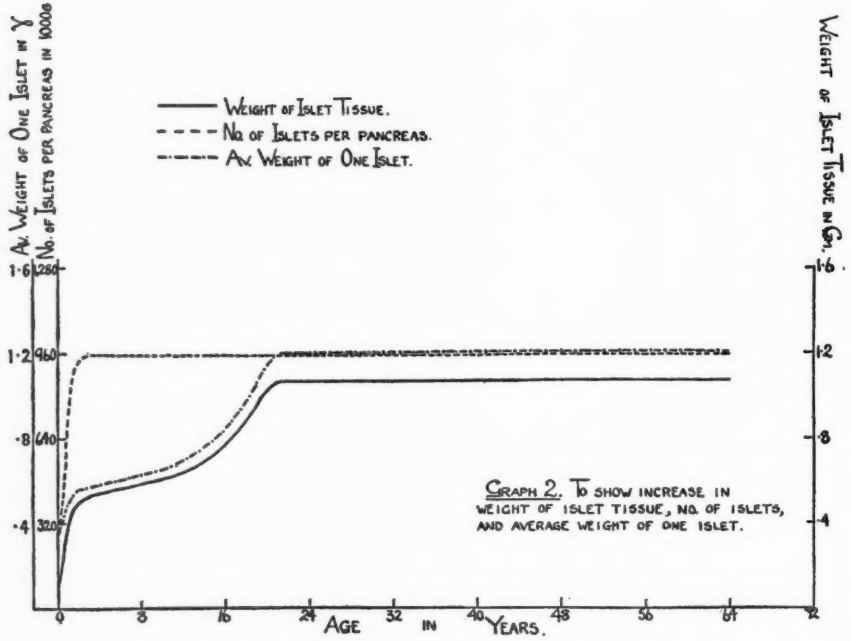
Graph 3 shows that in the first year of life the acinar and islet tissue equal each other in growth to the extent of increasing 3.5 times while the body as a whole increases only 2.2 times. It is, of course, recognized that this last figure is low since the body-weight is generally considered to treble itself in the first year of life. In the second year the rate of growth is considerably less, but the acinar and islet tissue still parallel each other ($\times 1.4$) and exceed body-growth ($\times 1.3$). This means that during the first two years the ductules differentiate equally into acini and islets. During the third year the growth rate is still less and a change in the relative rates

TABLE II

No.	Sex.	Age.	Wt. of body in kg.	Wt. of pan- creas in grm.	Wt. of acinar tissue in grm.	Wt. of acinar tissue per kg. body wt. in grm.	Wt. of islet tissue in grm.	Wt. of islet tissue per kg. body wt. in grm.	Average wt. of one islet in γ .	No. of islets.
1	F.	Still-born.	3.0	2.42	2.30	0.77	0.12	0.052	1.476	105,014
2	F.	Died at birth.	4.3	4.08	3.97	0.90	0.11	0.026	0.421	263,658
3	F.	Still-born.	3.2	2.40	2.35	0.73	0.05	0.015	0.344	139,535
4	F.	Still-born.	3.6	2.30	2.11	0.60	0.19	0.053	0.447	425,056
5	M.	Still-born.	3.3	1.92	1.83	0.56	0.09	0.027	0.185	486,486
6	M.	2 days.	3.3	3.04	2.92	0.89	0.12	0.035	0.508	236,220
7	M.	6 days.	2.9	1.47	1.41	0.49	0.06	0.021	0.508	118,110
8	F.	5 wks.	3.5	6.77	6.50	1.86	0.27	0.079	0.539	513,915
9	F.	9 wks.	3.5	2.75	2.66	0.76	0.09	0.026	0.237	379,747
10	F.	3 mths.	3.3	3.61	3.54	1.07	0.07	0.021	0.366	185,792
11	F.	4 mths.	4.3	5.10	4.86	1.13	0.24	0.056	0.275	876,364
12	M.	5 mths.	10.2	4.77	4.53	0.44	0.24	0.024	0.344	709,302
13	F.	6 mths.	5.0	4.99	4.88	0.98	0.11	0.022	0.421	263,658
14	M.	6 mths.	5.9	5.94	5.72	0.97	0.18	0.031	0.237	772,152
15	F.	6 mths.	5.5	9.04	8.83	1.61	0.21	0.039	0.715	296,503
16	F.	7 mths.	7.3	12.60	11.93	1.73	0.67	0.092	1.296	513,846
17	F.	7 mths.	5.1	6.20	6.00	1.18	0.20	0.039	0.220	900,000
18	F.	7 mths.	5.0	3.65	3.55	0.71	0.10	0.021	0.254	405,512
19	F.	8 mths.	5.5	4.42	4.22	0.77	0.20	0.038	0.508	393,701
20	M.	8 mths.	6.5	12.78	12.31	1.89	0.47	0.073	0.203	2,325,123
21	F.	9 mths.	9.5	13.23	12.77	1.34	0.46	0.049	0.680	679,412
22	M.	9 mths.	7.7	7.33	7.14	0.95	0.19	0.024	0.169	1,100,592
23	F.	10 mths.	6.7	11.90	11.45	1.70	0.55	0.082	0.607	909,390
24	M.	10 mths.	9.6	10.32	9.90	1.03	0.42	0.044	0.572	739,510
25	F.	1 yr.	6.9	9.02	8.84	1.28	0.18	0.026	0.392	454,082
26	F.	1 yr.	7.4	7.42	7.21	0.97	0.21	0.029	1.817	117,226
27	M.	1 yr.	9.1	9.96	9.63	1.06	0.33	0.037	0.392	841,837
28	F.	1 $\frac{1}{12}$ yr.	7.7	12.80	12.37	1.60	0.43	0.056	0.607	708,402
29	F.	1 $\frac{1}{12}$ yr.	9.1	9.83	9.49	1.04	0.34	0.037	0.642	529,595
30	F.	1 $\frac{1}{12}$ yr.	6.6	8.70	8.29	1.26	0.41	0.062	0.275	1,483,638
31	M.	1 $\frac{3}{12}$ yr.	7.8	8.10	7.83	1.00	0.27	0.034	0.447	597,315
32	F.	1 $\frac{3}{12}$ yr.	8.2	13.15	12.53	1.53	0.62	0.075	0.644	959,627
33	F.	1 $\frac{5}{12}$ yr.	10.3	17.60	16.98	1.65	0.62	0.061	0.508	1,220,472
34	F.	1 $\frac{5}{12}$ yr.	8.9	11.89	11.18	1.26	0.71	0.080	1.240	572,581
35	M.	1 $\frac{5}{12}$ yr.	9.4	8.45	8.23	0.88	0.22	0.023	0.254	854,331
36	M.	1 $\frac{5}{12}$ yr.	10.8	14.49	14.07	1.30	0.42	0.039	0.237	1,763,713
37	F.	2 $\frac{1}{12}$ yr.	10.6	13.64	13.52	1.28	0.12	0.011	0.680	176,471
38	M.	2 $\frac{1}{12}$ yr.	12.7	19.30	18.66	1.47	0.64	0.050	0.840	755,952
39	M.	2 $\frac{3}{12}$ yr.	9.9	21.56	20.78	2.10	0.78	0.080	0.715	1,090,909
40	M.	2 $\frac{3}{12}$ yr.	12.2	15.60	14.84	1.22	0.76	0.062	0.642	1,185,358
41	M.	3 yrs.	10.6	12.76	12.54	1.19	0.22	0.021	0.476	457,983
42	F.	5 yrs.	16.0	28.60	28.17	1.76	0.43	0.027	0.447	961,969
43	M.	5 yrs.	15.5	19.60	19.21	1.24	0.39	0.025	0.421	926,366
44	M.	5 yrs.	16.0	24.30	23.7	1.48	0.60	0.038	0.607	988,468
45	M.	6 yrs.	14.0	23.00	22.4	1.60	0.60	0.043	0.758	791,557
46	M.	6 yrs.	20.5	20.60	20.2	0.99	0.40	0.020	0.254	1,574,803
47	F.	6 yrs.	15.5	22.70	21.87	1.41	0.83	0.054	0.478	1,736,402
48	M.	7 yrs.	17.0	42.10	41.65	2.45	0.45	0.026	0.421	1,068,884

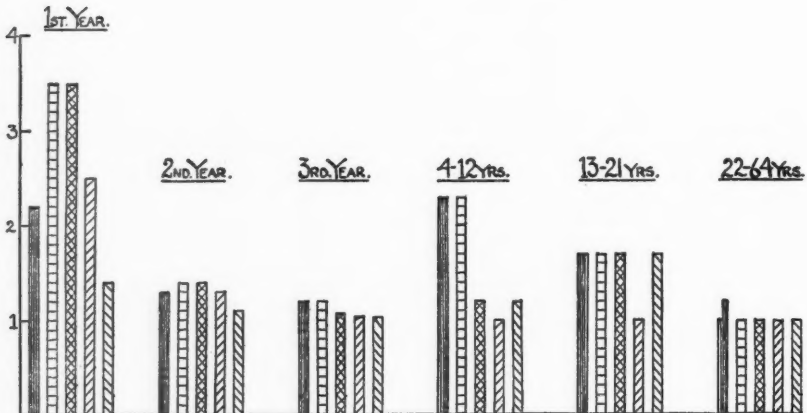
TABLE II (continued)

No.	Sex.	Age.	Wt. of body in kg.	Wt. of pan- creas in grm.	Wt. of acinar tissue in grm.	Wt. of acinar tissue per kg. body wt. in grm.	Wt. of islet tissue in grm.	Wt. of islet tissue per kg. body wt. in grm.	Average wt. of one islet in γ .	No. of islets.
49	M.	10 yrs.	25.5	21.40	21.05	0.81	0.35	0.014	0.344	1,017,442
50	F.	13 yrs.	25.0	28.60	27.90	1.12	0.70	0.028	1.025	679,612
51	M.	13 yrs.	33.0	58.80	58.25	1.76	0.55	0.017	0.715	783,217
52	M.	13 yrs.	52.5	44.60	43.54	0.83	1.06	0.020	0.644	1,645,963
53	F.	14 yrs.	34.0	55.50	54.91	1.62	0.59	0.017	0.643	917,574
54	M.	14 yrs.	46.5	56.60	55.87	1.20	0.73	0.016	1.184	618,644
55	F.	15 yrs.	37.0	40.50	39.28	1.06	1.22	0.033	1.240	983,871
56	M.	15 yrs.	40.5	35.10	34.49	0.85	0.61	0.015	0.930	655,914
57	F.	15 yrs.	48.0	46.20	45.35	0.94	0.85	0.017	0.715	1,188,951
58	F.	15 yrs.	40.5	51.80	51.18	1.26	0.62	0.015	0.644	962,733
59	F.	15 yrs.	43.5	78.30	76.87	1.77	1.43	0.033	1.240	1,153,226
60	F.	16 yrs.	42.0	50.20	49.58	1.18	0.62	0.015	0.572	1,083,916
61	M.	18 yrs.	33.0	59.90	59.12	1.79	0.77	0.023	1.076	712,963
62	F.	18 yrs.	50.0	79.80	78.49	1.57	1.31	0.026	1.240	1,056,532
63	F.	18 yrs.	50.0	49.00	48.56	0.97	0.44	0.009	0.680	647,059
64	F.	19 yrs.	49.5	44.70	44.13	0.89	0.57	0.011	0.840	678,571
65	M.	19 yrs.	64.5	90.40	90.36	1.39	1.04	0.016	0.447	232,662
66	F.	19 yrs.	48.0	52.00	51.08	1.06	0.92	0.019	0.978	940,695
67	F.	20 yrs.	57.5	77.50	77.15	1.32	1.35	0.023	0.715	1,888,112
68	F.	21 yrs.	50.0	61.60	59.79	1.20	1.81	0.036	1.416	1,274,648
69	F.	22 yrs.	50.5	88.00	85.94	1.70	2.06	0.041	1.476	1,391,892
70	F.	23 yrs.	43.0	52.90	52.41	1.22	0.49	0.011	0.680	720,588
71	M.	24 yrs.	48.0	100.50	97.18	2.05	2.32	0.048	2.738	846,715
72	M.	24 yrs.	38.0	63.00	61.90	1.63	1.10	0.029	0.478	2,301,255
73	F.	24 yrs.	37.0	45.00	44.28	1.20	0.72	0.019	1.476	486,486
74	F.	25 yrs.	44.0	49.50	48.66	1.11	0.84	0.019	1.128	743,363
75	F.	25 yrs.	46.0	88.00	87.45	1.90	0.55	0.012	0.758	725,594
76	M.	28 yrs.	56.0	61.20	60.63	1.08	0.57	0.010	0.715	797,203
77	M.	28 yrs.	55.0	79.10	77.81	1.42	1.29	0.023	1.351	955,555
78	F.	28 yrs.	53.0	67.00	65.74	1.24	1.26	0.024	2.122	594,340
79	M.	33 yrs.	52.0	79.50	77.67	1.49	1.83	0.035	1.744	1,051,149
80	F.	35 yrs.	60.0	67.90	66.98	1.12	0.62	0.010	0.392	1,581,633
81	F.	39 yrs.	48.5	76.10	75.28	1.55	0.82	0.017	0.758	1,018,794
82	F.	39 yrs.	37.0	88.00	86.62	2.34	1.38	0.037	1.817	758,242
83	M.	40 yrs.	46.0	79.80	78.69	1.71	1.11	0.024	0.840	1,321,429
84	F.	40 yrs.	51.0	66.00	64.79	1.27	1.21	0.024	1.817	664,835
85	F.	40 yrs.	40.5	41.80	40.64	1.00	1.16	0.029	1.416	816,901
86	F.	41 yrs.	43.0	58.60	58.28	1.35	0.32	0.007	0.930	344,086
87	F.	41 yrs.	53.0	50.30	49.15	0.93	1.15	0.022	1.351	851,852
88	F.	42 yrs.	36.0	58.60	58.22	1.62	0.38	0.010	1.184	322,034
89	M.	44 yrs.	48.0	70.00	69.55	1.45	0.45	0.009	0.883	509,627
90	F.	47 yrs.	48.0	61.90	60.62	1.26	1.28	0.027	1.918	666,666
91	M.	49 yrs.	49.0	56.50	55.49	1.13	1.01	0.021	1.476	684,282
92	M.	50 yrs.	54.0	74.50	73.54	1.36	0.96	0.018	0.978	981,595
93	F.	50 yrs.	51.0	74.70	73.32	1.44	1.38	0.027	9.78	1,411,043
94	F.	50 yrs.	53.0	67.20	66.39	1.25	0.81	0.015	1.076	750,000
95	F.	52 yrs.	46.0	46.30	45.05	0.98	1.25	0.027	1.240	1,008,065
96	M.	56 yrs.	57.0	61.30	60.21	1.06	1.09	0.019	0.715	1,524,477
97	M.	57 yrs.	52.5	94.20	93.06	1.77	1.14	0.022	0.840	1,357,142
98	M.	57 yrs.	64.5	95.20	93.35	1.45	1.85	0.029	0.978	1,891,616
99	F.	61 yrs.	53.5	71.80	70.94	1.33	0.86	0.016	0.978	879,346
100	M.	64 yrs.	49.5	63.60	62.44	1.26	1.16	0.023	0.930	1,247,312



- WEIGHT OF BODY.
- WEIGHT OF ACINAR TISSUE.
- ⊗ WEIGHT OF ISLET TISSUE.
- ⊠ NO. OF ISLETS.
- ▨ AV. WEIGHT OF ONE ISLET.

GRAPH 3. To show relative increase in weight of body, acinar and islet tissue, and in no. of islets and average weight of one islet.



of growth manifests itself in that the increase in body-weight equals that of the acinar tissue ($\times 1.2$) while the islet tissue has fallen slightly but definitely behind ($\times 1.06$). In other words, differentiation into islets is now a less marked feature. The same relation is maintained during childhood when the body and the acinar tissue exhibit parallel rates of growth ($\times 2.3$) while the islet tissue increases only 1.2 times. During adolescence the

TABLE III

To Show Relative Increase in Weight of Body, Acinar and Islet Tissue, and in the Number of Islets and Average Weight of One Islet.

Years.	1st	2nd	3rd	4-12	13-21	22-64
Body weight	2.2	1.3	1.2	2.3	1.7	1.2)
Weight of acinar tissue	3.5	1.4	1.2	2.3	1.7	1.0
Weight of islet tissue	3.5	1.4	1.06	1.2	1.7	1.0
No. of islets	2.5	1.3	1.03	1.0	1.0	1.0
Average weight of one islet	1.4	1.1	1.02	1.2	1.7	1.0

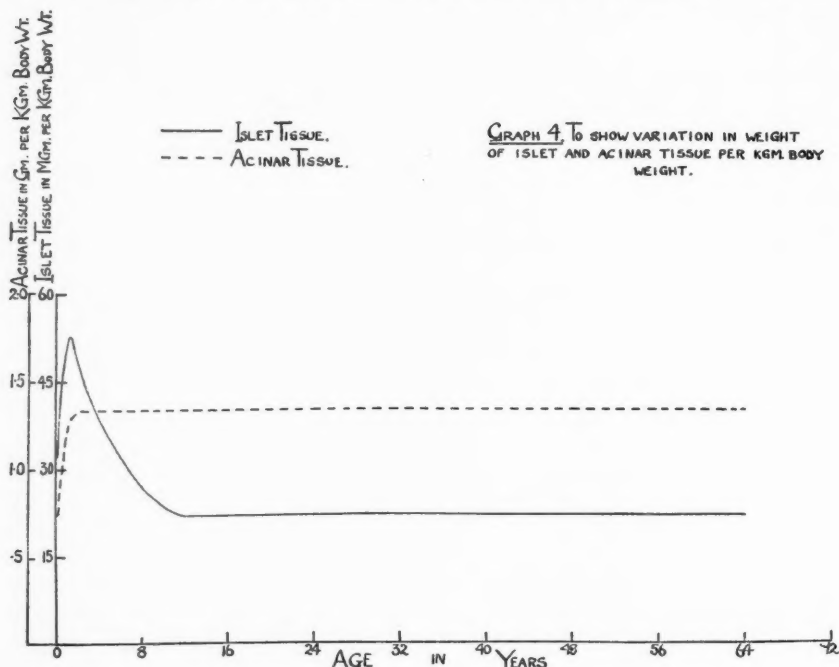
islet tissue reassumes a more rapid rate of growth to equal that of the body and acinar tissue, all increasing 1.7 times. After 21 years of age the three factors are, of course, stable except for the already-mentioned increase in body-weight during the later years of life.

As Graph 4 shows, from an average at birth of 0.74 grm. per kg. of body-weight the acinar tissue increases rapidly during the first year, diminishes quickly in its rate of increase during the second year and becomes stabilized early in the third year at 1.33 grm. It would thus appear that the milk diet of the infant creates a demand for digestive juices which stimulates the pancreatic acinar tissue to exceed body growth by a considerable margin. This rapid acinar growth is maintained by the dietetic changes, quantitative and qualitative, which occur after weaning, but the beginning of the third year sees a subsidence in the rate of acinar growth so that thereafter the body and acinar tissue develop *pari passu*.

2. *Number of islets.* While several investigators (Opie (17); Sauerbeck (19); Heiberg (8); Cecil (4)) have made counts of the islets in specified sectional areas of human pancreas, Clark (5) alone has computed the total number of islets in the human pancreas. He did so by employing the technique which Bensley (1) had devised for estimating the total islet-count in the guinea-pig's pancreas—transfusing the organ immediately after death with neutral red or janus green which selectively stain the islands, under a low power of the microscope counting the islands in several teased slices from the head, body, and tail, weighing these and calculating the total number of islets according to the weight of the whole pancreas. In seven subjects varying in age from half a year to 45 years he obtained counts between 120,000 and 1,760,000. Clark entertained hopes that this method might be employed on autopsy subjects, but attempts at transfusion on four subjects recently dead gave such discouraging results that he considered the method inapplicable to all except subjects dead by violence.

The mathematical method above described has, therefore, an advantage

over Bensley's technique in that it is applicable to post-mortem material and its employment has made it possible to obtain estimates of the islets in a reasonably large series of cases. The fact, moreover, that the series covers the age-period from birth to 64 years has afforded an opportunity of determining whether the islets of Langerhans actually increase in number after birth. Regarding this question the literature is confusing. Laguesse



(10) states that at birth the islets of Langerhans are fewer than during foetal life, and that after birth the islets undergo further diminution in number. Opie (17), on the other hand, considers that after birth the islets remain constant in number and merely become separated by a growth of acinar tissue. The final alternative is expressed by Weichselbaum and Kyrle (21) who postulate that new formation of islands from ducts does not cease during foetal life since these structures in the adult organ may be found continuous with ducts of which cells are undergoing mitosis.

Table II shows five still-born infants with counts varying between 105,014 and 486,486, the average being 284,000. From this level Graph 2 demonstrates a rapid rise in the total count which is maintained throughout the first two years. Graph 3 shows that the increase is 2.5 times in the first and 1.5 times in the second year. During the third year the rate of increase rapidly falls away ($\times 1.03$) until the count becomes stabilized at 960,000. So far as is known, this is the first time the islets have been shown to increase in number after birth, and as is seen the increase is a marked

one amounting to 3.4 times during the first three years. In the original graph, moreover, it is seen that the variation in total islet-count at all age-periods is, indeed, remarkable. Thus, at eight months two cases (19 and 20) occur with counts of respectively 393,701 and 2,325,123, while at 24 years there are two cases (73 and 72) with respectively 486,486 and 2,301,255.

3. *Weight of average island.* No increase occurs in the number of islands after the third year, yet the total weight of islet tissue, it has already been seen, continues to increase thereafter. The deduction is that this increase is effected by enlargement of the existing islands. Table II indicates that the average weight of the islands at birth (excluding Case 1 which is apparently exceptional) is .350 γ . From this level Graphs 2 and 3 show that the weight of the average island increases rapidly during the first year ($\times 1.4$) while in the second and third years the rate of growth becomes progressively less ($\times 1.1$ and $\times 1.02$ respectively). A slow rate of growth is maintained during childhood ($\times 1.2$), but adolescence is again characterized by a more rapid increase in the weight of the average island ($\times 1.7$). This hypertrophy is, indeed, such that it enables the islet tissue as a whole to parallel the body and acinar tissue in their growth-rate. As in the case of the two factors last mentioned, the growth of the islets slows down toward, and becomes finally stabilized at, the age of 21 years about 1.2 γ . Between birth and 21 years the increase in weight of the average island is thus about 3.4 times which, it will be remembered, is the extent to which the islets increase in number during the first three years. Finally Table II shows that the variation in islet-weight is at all ages considerable. Thus Cases 25 and 26 at one year have average islets weighing .392 γ and 1.817 γ respectively, while at 24 years Cases 72 and 71 have islets of respectively .478 γ and 2.738 γ .

At this stage Graph 3 and Table III are instructive in that they illustrate the extent to which the increase of islet tissue is accounted for by an increase in the number of islands and in the weight of the average island. In the first year of life the islet-tissue increase is seen to be due more to an increase in the number of islands ($\times 2.5$) than in the weight of the individual islands ($\times 1.4$). In the second year while growth-rate is much less the increase in number ($\times 1.3$) still exceeds the increase in size ($\times 1.1$). In the third year there is little difference between the degrees of hyperplasia and hypertrophy, but the former is still slightly in the van— $\times 1.03$ as against $\times 1.02$. During childhood and adolescence the increase of islet tissue is effected wholly by simple enlargement of the islands, but while in childhood the islet-hypertrophy does not keep pace with that of the body and acinar tissue, in adolescence the enlargement of the islets proceeds at the same rate as the weight-increase of these other two factors. At 21 years the islet-hypertrophy ceases and the islet tissue as a whole becomes stabilized.

A graph was constructed to reveal the relationship between the size and number of islands. This shows that when the number of islands is small

the size of the average island is *as a rule* also small. When there is a medium number of islands the average island may be of either small or large size. Finally, a large number of islands is associated with islands the average size of which tends to be small.

4. *Sugar tolerance.* It has been shown by several investigators that the tolerance of infants for sugar is definitely higher than that of adults. Thus, Mogwitz (14) estimating sugar tolerance in six children between four and thirteen months fed five with milk which provided about 2 grm. sugar per kg. body-weight. In four of these there was but little response, the blood-sugar curve rising at the most 17 mg. per cent. while the curve-peaks of the other cases were 124 and 134 mg. per cent. Bergmarck (2) investigated the response of the blood-sugar to the ingestion of various sugars in infants. He claims that saccharose produced a higher response than maltose and maltose than lactose, but all the resultant curves were much lower than those of adults. After estimating the blood-sugar curves of a series of infants and normal adults, Spence (20) makes the statement that in children under three years of age a low blood-sugar curve must be taken as the expression of the normal sugar tolerance. Brown (3) arrived at a similar conclusion after an investigation of 10 healthy infants under thirteen months.

This unusual activity on the part of the carbohydrate storage mechanism in young children suggested that the ingestion of sugar stimulates a relatively greater secretion of insulin in them than in adults, and it therefore seemed logical to deduce that the explanation of this hypersecretion might be found in the presence in the infant pancreas of an amount of islet-tissue relatively greater than is found in the adult organ. This entailed the calculation in each case of the weight of islet-tissue per kg. body-weight and the relation of this figure to age is shown in Graph 4.

This graph indicates that from an average of 32 mg. per kg. body-weight at birth the islet-tissue increases rapidly to reach a maximum of 53 mg. per kg. at the end of one and half years. Attention has of course already been drawn to the fact that the body-weight in this series of cases increases only in 2.2 times in the first year, as against the normal three times, a deficiency due in all probability to some emaciation of the subjects at the end of the first year. It is likely, therefore, that the increase of islet-tissue per kg. body-weight during the first one and half years is less marked than indicated by the graph. Thereafter the amount falls, rapidly at first, less rapidly later, and becomes stabilized about the age of twelve at 22 mg. per kg. It is thus seen that the years of high sugar tolerance, i.e. the first three years according to Spence, constitute a period when the body has a relatively high content of islet tissue. The discovery of this correlation suggests that the rapid absorption of sugar from the blood of infants is due to the stimulation of a relatively large amount of islet tissue whereby a correspondingly large quantity of insulin is secreted and the rising blood-sugar is prevented from reaching the higher adult level.

Pursuing this argument Graph 3 would indicate that sugar tolerance should increase during the first one and half years of life and decrease during childhood to reach the adult standard at puberty. Regarding the early increase in tolerance neither of the series investigated by Spence and Brown affords supporting evidence, but their cases after all are few (6 and 10 respectively). Regarding tolerance in childhood, Spence states that after the age of three years the curve is of the adult type, but he bases this conclusion on only four cases between four and seven years. The high curves he obtained might well have been given by cases which chanced to have a relatively low islet-tissue content. Graph 4 suggests that throughout childhood sugar tolerance falls steadily until puberty, and it is believed that investigation of a sufficient series would prove this possibility. Unfortunately no series of cases has been found which covers this period.

It is well known that sugar tolerance diminishes with age (Marshall (13); Hale-White and Payne (6); Ogilvie (16)); but Graph 3 shows that during the later years of life the amount of islet tissue per kilogramme body-weight remains constant. Therefore, the deterioration of sugar tolerance in the later years would appear to be due to a gradual physiological failure in the secretion of insulin, an exaggeration of which failure sometimes causes the elderly subject to become mildly diabetic. It is of course realized that the explanation of this late deterioration in sugar tolerance may lie primarily, not in the islet tissue, but in the anterior pituitary which has of late been shown to be closely related to the islet tissue and carbohydrate metabolism (Houssay and Biasotti (7)).

Summary

Methods are described whereby, given the weight of a pancreas, estimates can be made of the following factors in the pancreas: (1) weight of acinar tissue; (2) weight of islet tissue; (3) weight of an average island; and (4) total number of islands.

Estimates of these factors have been made in 100 pancreases obtained from subjects (59 female and 41 male) varying between newly-born infants and an adult, 64 years of age, all of whom appeared *post mortem* to be of normal weight.

Graphs have been constructed covering the age-period above-mentioned to show the increase in weight of the body, of the pancreatic acinar, and islet tissue, and in the size and number of the islands. A graph (4) is also given illustrating the rates of increase of these factors relative to each other.

It is shown that the infant pancreas contains a relatively greater quantity of islet tissue than the adult organ and it is suggested that this finding explains the higher tolerance for sugar which obtains in the earliest years of life.

I wish to express my thanks to Dr. Agnes Macgregor for supplying me with the infant pancreases investigated in this research and also to Prof. A. Murray Drennan, Dr. W. G. Millar, and Dr. C. P. Stewart for helpful criticism.

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THE SECOND POSITIVE WAVE OF THE QRS COMPLEX¹

BY A. HOPE GOSSE AND T. E. LOWE

With Plate 10

Introduction

INVESTIGATIONS have been published, in recent writings, of the variations, from the average normal, of the ventricular complex in the electrocardiogram. Generally these variations have been taken to indicate myocardial damage.

The present investigation is confined to those electrocardiograms showing the occurrence of a second positive wave, associated with a definite R and a marked S-wave, in the ventricular complex in Lead III. This has been described by Katz and Slater, and associated by them with myocardial damage in some 86 per cent. of cases.

Our series is taken from patients between January 1930 and July 1935, referred by practitioners for an opinion on their cardiac condition, usually because of symptoms referable to the heart, sometimes for the interpretation of cardiac murmurs or for a general overhaul. As a consequence of these conditions, the majority of the patients are in the middle or later years of life. In all, an electrocardiogram and an X-ray of the heart were taken as a routine part of a full clinical examination.

Investigation

A total number of 2,045 cases were examined, and the following series of 44 electrocardiograms selected. The criteria of selection were four in number.

1. The presence of a definite R-wave in Lead III.
 2. The presence of a subsequent S-wave.
 3. The presence of a definite second positive wave following S.
 4. The persistence of all of these waves in all of the complexes of the tracing.
- A typical example is illustrated.

The last condition was found to be essential, because frequently either the R or the second positive wave, after both being present for two or more complexes, would disappear. This was found to be a respiratory variation.

The size of the heart was determined in every case by the measurement of its maximum diameter on a film taken with the tube at a distance of four feet. Any measurement up to, but not exceeding, six inches in the greatest diameter was regarded as being within normal limits.

¹ Received April 6, 1937.

No.	Sex.	Age.	Outstanding symptoms.	Heart size in inches.	B.P.		Electro-cardiogram.	Clinical diagnosis.
					S.	D.		
1	M.	55	Effort precordial pain, 500 yards walk.	5½	120	80	Left ventricular preponderance.	Angina pectoris.
2	M.	35	Insurance examination.	5½	120	70	Left ventricular preponderance.	Normal heart.
3	M.	47	Continuous epigastric pain.	5½	115	70	L.V.P. T3 inverted.	Normal heart.
4	F.	62	Dyspnoea, occasional effort precordial pain, secondary anaemia.	5½	195	80	Normal.	Peptic ulcer, hypertension.
5	F.	66	Lumbar pain, haematuria.	4½	130	80	P.V.C. T3 inverted.	Renal calculus.
6	M.	69	Senility.	5½	155	90	R1 and R2 notched.	Normal heart.
7	M.	74	Dyspnoea in winter.	5½	140	85	R2 notched.	Normal heart, emphysema, bronchitis.
8	M.	57	Lassitude.	6	140	100	T3 inverted.	Normal heart.
9	M.	72	Effort pain.	6	160	100	Normal.	Angina pectoris.
10	M.	81	Dyspnoea.	5½	135	85	L.V.P. T3 inverted.	Normal heart.
11	M.	55	Dyspnoea, cough, sputum, albumin in urine.	6½	190	120	Normal.	Ch. nephritis, collapsed lobe of lung.
12	M.	61	Precordial pain.	5½	150	90	Normal.	Normal heart; fibrositis.
13	F.	59	Dyspnoea, chest pain.	5	130	80	Normal.	Normal heart; peptic ulcer.
14	M.	55	Dizziness and giddiness.	5½	125	75	Slight L.V.P.	Normal heart.
15	M.	56	Obesity.	6	135	85	L.V.P. T3 absent.	Normal heart.
16	M.	71	Irregularity of heart beats.	5½	115	80	Slight L.V.P.	Normal heart.
17	M.	61	Dyspnoea and oedema of legs.	5½	150	90	Normal.	Normal heart, emphysema.
18	F.	65	Effort pain.	5½	150	100	Slight L.V.P.	Angina pectoris.
19	F.	60	Dyspnoea and effort pain.	6	150	90	L.V.P. T1 and T2 inverted.	Angina pectoris.
20	M.	65	Dyspnoea.	5½	160	100	Normal.	Normal heart; emphysema.
21	M.	36	Insurance examination.	6½	170	80	L.V.P.	Aortic incompetence.
22	M.	66	Slowness of heart beats.	5½	120	90	L.V.P.	Normal heart.
23	M.	60	Dyspnoea.	7½	205	90	L.V.P. sino-audicular block present.	Hypertension, congestive failure, pulm. tub.
24	M.	11	Convalescent from influenza.	3½	—	—	T3 inverted.	Simple tachycardia.
25	M.	57	Dyspnoea.	6	190	120	T3 inverted.	Hypertension, emphysema.
26	F.	53	Effort precordial pain.	5½	165	95	L.V.P. T3 inverted.	Angina pectoris.
27	M.	64	Fluttering of the heart.	5½	140	90	Slight L.V.P. T3 inverted.	Normal heart.
28	M.	48	Effort precordial pain.	6½	130	90	L.V.P. T3 inverted.	Angina pectoris.

No.	Sex.	Age.	Outstanding symptoms.	Heart size in inches.	B.P.		Electro-cardiogram.	Clinical diagnosis.
					S.	D.		
29	M.	52	Syncopal attacks.	6½	145	100	T3 inverted. P.V.C. present.	Myocardial degeneration, pulsus alternans.
30	M.	77	Dyspnoea.	6	170	110	L.V.P. Escape of ventricle.	Normal heart; atheroma.
31	F.	76	Effort precordial pain.	5½	135	90	L.V.P. T3 inverted.	Angina pectoris.
32	M.	74	Substernal pain.	4½	140	80	T3 inverted.	Angina pectoris.
33	M.	66	Effort precordial pain.	6½	195	110	L.V.P. T3 inverted.	Angina pectoris, aortic incompetence.
34	M.	49	Dyspnoea.	6½	—	—	Auricular fibrillation.	Auricular fibrillation.
35	F.	62	Precordial discomfort, obesity.	5½	125	85	L.V.P.	Normal heart, obesity.
36	M.	66	Dyspnoea.	6½	170	90	L.V.P. PR. 6/25th sec. Wide QRS.	Myocardial degeneration; renal calculus.
37	M.	43	Effort dyspnoea, palpitations.	5½	—	—	Auricular fibrillation.	Auricular fibrillation.
38	M.	59	Effort dyspnoea, Wasserman positive.	7	185	105	L.V.P.	Syph. aortitis; myocardial degeneration.
39	F.	23	Effort dyspnoea.	5½	—	—	T3 inverted.	Normal heart.
40	M.	59	Irregularity of heart beats.	6	160	105	T3 inverted. L.V.P., P.V.C.s present.	Normal heart.
41	M.	13	Occasional pain in left side.	4	—	—	T3 inverted.	Congenital heart.
42	F.	6	Systolic murmur heard on auscultation.	4½	—	—	Normal.	Congenital heart.
43	F.	38	Precordial pain, cough.	4½	—	—	Slight L.V.P.	Normal heart.
44	M.	38	Effort precordial pain.	5	180	100	Normal.	Angina pectoris.

Abbreviations:

P.V.C. = Premature ventricular contractions.

L.V.P. = Left ventricle preponderance.

Discussion

Analysing these figures it will be noted that in one case, No. 23, the second positive wave was absent at a subsequent examination three months later. In No. 37 it was present both when the auricle was fibrillating and when the rhythm was normal. In No. 29 there was in addition a second negative wave. In only 23 cases was there left ventricular preponderance present.

Of these 44 cases in the series, 23 had hearts which were considered to be normal clinically. Left ventricle preponderance alone has not been considered evidence of cardiac disease. Nineteen had evidence of myocardial damage and two were thought to be congenitally abnormal.

The cases of cardiac disease were:—

Angina pectoris	9 cases.
Hyperpiesia	3 „
Auricular fibrillation	2 „
Aortic regurgitation	2 „
Pulsus alternans	1 case.
Syph. aortitis	1 „
Myocardial degeneration	1 „
Total	19 cases.

It was not possible from our records to determine accurately the total number of cases of the individual lesions seen in the period under review, but we can state that:—(1) The complex was present in less than one in every 10 cases of angina pectoris. (2) The complex was present in less than one in every 10 cases of myocardial damage associated with pulsus alternans. (3) The complex was present in less than one in every 40 cases of auricular fibrillation, and (4) It was not seen in 40 cases of bundle-branch block.

Summary

1. An analysis of 44 cases, from a series of 2,045 cases, which showed a second positive wave in the ventricular complex of Lead III has been made.
2. The complex occurred in 2.2 per cent. of all heart cases.
3. Of this 2.2 per cent the cases were almost equally divided between hearts diagnosed as clinically normal and those in which myocardial damage was considered to be present.
4. The complex was only rarely present in a large number of cases in which there was ample clinical evidence of myocardial damage.

Conclusions

As a result of this investigation we do not find that any diagnostic importance can as yet be placed upon this variation from the average normal ventricular complex.

We are aware that this is a negative finding, but we feel that any claim for diagnostic significance of any variation from the normal should be treated critically.

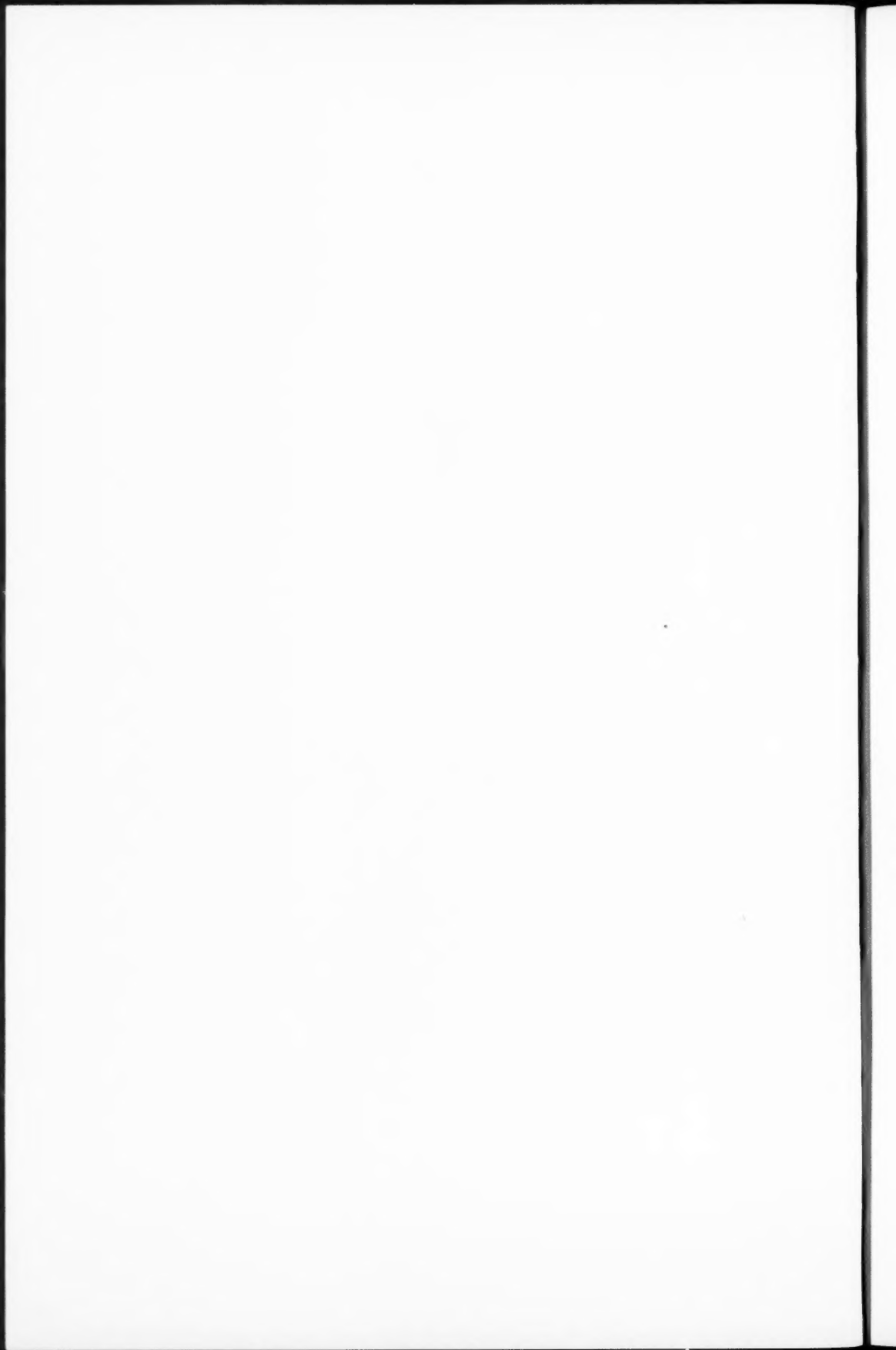
We have not been encouraged to view any of these cases in a more serious light since our attention was directed to the variation described by the authors mentioned.

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An example of the second positive R wave in the ventricular complex of Lead 3



PORPHYRINURIA IN PELLAGRA¹

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Introduction

IN recent years the study of pellagra has received a new impetus, especially in the United States, through the investigations of Goldberger (20, 21), Ruffin and Smith (37), Sebrell (42) and others. The etiology of the disease as well as the significance of the various symptoms found in this condition are still unsolved problems. The symptoms most frequently observed are those present in the skin, gastro-intestinal tract, and central nervous system, as well as anaemia. All of these may occur together, but frequently only a few are seen in one case. The appearance of the disease seems to vary even geographically. The fact that the skin lesions may be totally absent in patients suffering from pellagra is becoming more appreciated. Nevertheless, the most obvious changes are those of the skin from which the disease derives its name.

There is a general consensus of opinion that pellagra is most commonly found in patients with a history of food intake deficient either qualitatively or quantitatively. The endemic type of pellagra occurs almost invariably among populations whose diet consists mainly of maize and maize products. The pellagra syndrome is also seen as a consequence of a quantitatively insufficient diet or in persons with chronic alcoholic addiction whose food intake has been very low. Symptoms of pellagra may also follow severe damage of the gastro-intestinal tract due to infectious diseases such as dysentery or tuberculosis, to operative interference or to neoplasm. The different types of non-endemic pellagra have sometimes been called 'secondary pellagra'. In explanation of the pellagra syndrome, the role of the deficiency of the vitamin B2 complex has been emphasized, and a deficient absorption of essential dietary elements seems at the moment to be the most likely cause of the syndrome.

One of the authors (P. E.) together with Edgar and Lucas (6) observed that rats deprived of the vitamin B2 complex excreted in the urine a coproporphyrin in high concentration which disappeared after addition to the diet of the constituents of the vitamin B2 complex (lactoflavin and the yeast, Fuller's earth, filtrate fraction). This fact is mentioned without prejudice to any possible arguments in favour of or against a relationship between the condition of vitamin B2 deficiency in rats and human pellagra.

¹ Received February 18, 1937.

Following these observations, Ellinger and Dojmi (7, 8) examined cases of endemic pellagra in Yugoslavia. These investigations have been briefly reported. Eight cases of endemic pellagra observed from the beginning of the disease to a more severe stage, showed an increased porphyrin excretion. In six, this excretion was greatest in the early stages and diminished later, even though the other symptoms became more severe and new ones began to appear. In only two cases was a high porphyrin excretion continued with an increasing severity of the symptoms; in these cases it disappeared simultaneously with healing. One case of freshly healed pellagra and 13 cases who had suffered from pellagra in the preceding year, showed no increased porphyrinuria above the small amounts found in healthy subjects

There is still much controversy concerning the significance of the various symptoms of pellagra. Of these the skin lesions still engage much attention. Spies observed a few years ago that pellagrins, while receiving a diet deficient in the vitamin B2 complex, may show a complete healing of the skin lesions. It has also been a frequent clinical observation, at least in the United States, that the dermatitis of pellagra may be confined to the perineal region of a fully clothed individual or that skin lesions may be entirely absent. These observations are important in that they show that the skin lesions cannot be relied upon as an index for diagnosis of pellagra in all cases or for the efficacy of treatment. In any attempt to assess the significance of the skin lesions the finding of porphyrinuria in pellagrins is therefore of great interest as it suggests that a relationship might exist between pellagra and an increased excretion of porphyrin in the urine. We stress *increased* porphyrin excretion because small amounts of coproporphyrin are regularly found in the urine of healthy individuals. An increased porphyrin excretion would give a satisfactory explanation of the skin lesions when present on the exposed parts of the body, as they might be brought about by a sensitization of the skin to light, caused by the porphyrin in the circulation. Fischer (13) as well as Kämmerer and Weisbecker (31) have shown that, compared with the severe and sudden effects of uroporphyrin, coproporphyrin produces a much less intense and acute sensitization to light. The relatively milder intensity of the skin lesions in pellagra would fit in with the hypothesis that in pellagra coproporphyrin is the sensitizing agent. But there is also a similarity between the clinical symptoms of pellagra and those of the acute porphyrinuria, and the presence of coproporphyrins in the body of pellagrins might explain many of the clinical symptoms.

To establish an increased urinary porphyrin excretion as an integral symptom of the pellagra syndrome would be a definite aid to the diagnosis of pellagra in its early stages. It seemed worth while therefore to obtain data on different types of pellagra, and an investigation of a series of predominantly alcoholic pellagrins together with an adequate number of controls, studied under carefully controlled conditions, is presented in this paper.

Material and Methods

Porphyrin analyses were done on urine specimens from a total number of 96 persons and two monkeys. Of these, 16 were active pellagrins and three were healed pellagrins. The controls consisted of 77 human beings and two monkeys.

Pellagra cases: Fifteen of the pellagrins were admitted to the medical service of Lakeside Hospital, Cleveland, U.S.A., between August 1935 and June 1936. Of these 15, 14 gave a history of high alcohol consumption and low food intake over a long period of time. One patient died shortly after entering the hospital but 14 could be followed through the course of the disease. One patient suffered from pellagra secondary to gastro-intestinal tuberculosis, as proved later by autopsy. Two of the admissions represented relapses in patients who had been in the hospital earlier in the course of the study. In addition to the cases of active pellagra, two patients are included who had recovered from a previous attack of pellagra for one and three years, respectively. We have also included two patients studied in London, one a cured case and one a case of secondary pellagra; these were not studied in such detail as the other cases.

The patients were kept, where possible, on a pellagra-producing diet containing 800 calories or less per day, for varying periods following admission to the hospital. They were then put on a high caloric, high-vitamin diet, supplemented in some instances by yeast given orally or by intramuscular administration of liver extract. On admission a 24-hour urine specimen was collected and the amount recorded. Similar specimens were obtained during the hospital stay at various representative stages of the disease. It must be remembered that in patients with severe diarrhoea the estimation of the amount of urine is quite inaccurate. In the collection of the urine any faecal contamination was rigorously excluded. Of each 24-hour urine specimen a sample contained in a large test-tube and sealed by means of a paraffined cork-stopper (no preservative being needed) was dispatched to the Lister Institute of Preventive Medicine, London, where within a few weeks after collection the analyses for porphyrins were carried out in duplicate by one of us (P. E.).

Controls: The 77 human controls consisted of three groups. Firstly, 18 healthy individuals, male and female; secondly, 49 cases suffering from the following diseases: mental disorders (such as schizophrenia) accompanied by loss of weight and nutritional disturbances; Korsakow's syndrome, peripheral neuritis of unknown origin, epilepsy, chronic diarrhoea and chronic colitis of unknown origin, idiopathic pruritus, diarrhoea and infantile eczema, pernicious anaemia and subacute combined sclerosis, eczematous dermatitis, macrocytic anaemia of unknown etiology, gastric ulcer, anaemia secondary to bleeding, malignant hypertension, idiopathic hypochromic anaemia, cirrhosis of the liver, Hodgkin's disease. From these two groups of controls one 24-hour urine specimen was collected and examined. Of the third group of ten control subjects, five were given intramuscular injections of liver on five succeeding days, and the other five individuals were given large amounts of yeast for a period of ten days. A 24-hour urine specimen was collected before the start of either medicament; a similar specimen was

again collected on the day following the last dose of liver and on the day of the last dosage of yeast, respectively. In addition, the urine of two monkeys with mild nutritional macrocytic anaemia was examined.

Method of porphyrin analysis: As the study of Ellinger and Dojmi (8) had included cases of pellagra occurring in rather inaccessible districts removed from well-equipped laboratories, and as in the present work the urine specimens were shipped over a great distance, it was necessary to devise a method which could be carried out with simple equipment, and which would give sufficiently accurate results with small amounts of urine. Furthermore, the method had to allow a fairly large series of estimations in a relatively short time. None of the examined urines contained recognizable amounts of porphyrins insoluble in ether—this was tested in each case—therefore a method was developed which was applicable to ether-soluble porphyrins only.

The methods for quantitative estimation of ether-soluble porphyrins have been discussed by Fikentscher and Franke (10, 11). They have described the following three different types of methods: spectro-photometric, colorimetric, fluorimetric. Of these the spectro-photometric was not practicable, as relatively large amounts of urine are required and considerable apparatus would be necessary. A colorimetric method described by Thiel (48) was criticized by Fikentscher and Franke (10, 11) because the porphyrin amounts estimated by this method were much higher than those found by other methods. According to these authors, this discrepancy was due to the presence of other red-stained substances in the acetic acid-ether extract of the urine, and to the use of an 'absolute colorimeter'. These objections were disproved by Thiel who showed that the high porphyrin values obtained were the consequence of an arithmetical error made in his first publication. Schreus and Carrié (39) have suggested another colorimetric method by which the porphyrin is estimated as tetrachlorporphyrin hydrochloride, but the instability of the green colour of this substance precludes the practical application of the method. Objections were raised by Fink and Hoerbuerger (12) against the principle of the fluorimetric estimation of porphyrins as developed by Fikentscher (9). One of the present authors (P. E.) was also unable to get reliable results with this type of method. A colorimetric method was therefore employed which differs in some ways from that described by Thiel (47).

A measured amount of urine (3–10 c.c.) was acidified with glacial acetic acid to a pH of about 4.0 and shaken with 5–20 c.c. of ether until no more porphyrin could be extracted. The ether was then washed repeatedly with water. A complete separation of the two layers was allowed to take place. To a measured fraction of the ether was added one-fifth of that amount of 25 per cent. of hydrochloric acid. On shaking, the porphyrin contained in the ether fraction was completely transferred to the hydrochloric acid which became stained purple, the intensity of the colour depending on the porphyrin concentration. The colorimetric estimation was made either in a colorimeter of the Dubosq-type against a standard solution of porphyrin or by comparison with porphyrin solutions of known concentration.¹ The time necessary for the complete transfer of the porphyrins from the urine into

¹ We were able to compare our own porphyrin standard solution with a solution of coproporphyrin I, kindly supplied by Geheimrat Professor Dr. H. Fischer, Munich through Professor R. Robison, and we should like to express our thanks to them.

ether and from the ether into hydrochloric acid differed in various specimens, being determined by the nature of the porphyrin present (whether free porphyrin, porphyrin ester, or leuco-compound). In most specimens the process was completed in half an hour, but as a check the colorimetric estimations were repeated after three hours and after twenty-four hours.

In some cases, beside the porphyrins, a yellowish-brown substance with urobilin-like properties and only one absorption band at 4,850 Å. U. in alkaline solution was present in the urine. Sometimes this yellow-brown material was found to increase when urine containing porphyrins was allowed to stand for several weeks. This fact suggests that the yellow-brown substance may be a product of degradation of porphyrin. Similar substances are reported by nearly all the workers (MacMunn (34). Hammarsten (27), Garrod and Hopkins (19), Schumm (41), Ellinger and Riesser (4), Loeffler (33), Fischer and Zerweck (15), Sachs (38), Grotepass (23) and others) who have studied porphyrin excretion in the urine. However, there is much confusion regarding these yellow-brown substances often found in porphyrin-containing urines. Our substance is not the normal brown urine pigment whose increased excretion in porphyrinuria was described by Fischer and Zerwecki (15) in a concentration proportional to the excreted porphyrin, this not being true of our substance. Also the pigment of Fischer and Zerweck (15) was not taken up by an acetic acid-ether extract as was the yellow substance we found sometimes present. It is more probable that the latter may be similar to that described by Heilmeyer (30). According to Fischer and Treibs (16) this substance as well as porphyrin may be formed from porphyrinogen through oxidation by various oxidizing agents, including the oxygen present in the air.

As this yellowish-brown substance, when present, interfered with the colorimetric determination of the porphyrins, it was necessary to remove it by shaking the ether solution repeatedly with a 20 per cent. solution of sodium carbonate. By this means porphyrins and yellow substance are both transferred into the alkaline solution, but on further shaking with glacial acetic acid and ether the porphyrins are transferred into the ether and most of the yellow substance remains in the aqueous solution. By repeating this process several times the ether solution of porphyrins can be completely freed from the yellowish-brown substance. It was not possible, however, to estimate the yellowish-brown substance quantitatively. If present in high concentration the result of the porphyrin estimation became inaccurate, giving too low a value. We have therefore marked in Table I the three instances where large amounts of this yellow substance were present. Even in the presence of small amounts of yellow substance the accuracy of the porphyrin estimation was diminished by the method employed for the removal of the yellow substance, causing a loss of porphyrins up to 10 per cent of the total. Therefore, we do not give the results of the porphyrin concentrations in units of weight. We mark concentrations below 0.1 mg./litre as 0:² between 0.1 mg./litre and 1 mg./litre as *: between 1 mg./litre and 10 mg./litre as **: between 10 mg./litre and 100 mg./litre

² Porphyrins when found in normal individuals occur in amounts up to 0.1 mg. per litre of urine. This is in agreement with the findings of Schreus and Carrié (40).

TABLES I AND II
TABLE I (*Alcoholic Cases*).

Case No.	Race.	Sex.	Date of urine collection.	Urine volume c.c./24 hrs.	RBC mill.	Hgb %	Body temp. (Highest/24 hrs.)	Pulse.	Diet.	Subjects receiving yeast or liver.	Skin lesions.	M.M. lesions.	Diarrhoea.	Porphy- rins in urine.
1	W.	M.	18.8.35	340	—	—	38.5	115	PP.	No	++	++	++	* Y.S.
			19.8.35	180	4.7	85	38.5	110	HV.	"	++	++	++	* Y.S.
			29.8.35	1,150	—	—	37.5	110	"	"	++	++	++	***
3	C.	F.	9.9.35	750	4.5	82	37.5	100	"	"	0	0	0	0
5	C.	F.	24.8.35	450	3.75	80	37.9	105	PP.	"	++	++	++	***
			2.10.35	700	3.87	76	37.8	95	"	"	++	++	++	***
			6.10.35	1,350	—	—	37.8	85	"	Yeast	++	++	++	***
6	C.	F.	11.10.35	2,400	3.6	72	37.5	80	HV.	"	0	0	0	0
			7.10.35	1,500	3.4	72	37.8	95	PP.	No	++	++	++	***
			12.10.35	1,450	—	—	37.5	85	"	"	++	++	++	0
7	C.	M.	25.10.35	800	3.7	78	37.5	80	"	Liver	0	0	0	0
			27.11.35	400	4.1	76	38.8	105	"	No	++	++	++	***
			3.12.35	850	—	—	37.8	100	HV.	Yeast + liver	++	++	++	***
			11.12.35	450	4.0	82	37.8	100	"	No	++	++	++	***
8	W.	M.	27.11.35	650	4.36	90	38.3	110	PP.	"	++	++	++	0
			2.12.35	850	—	—	37.7	100	HV.	"	++	++	++	***
			8.12.35	1,000	4.66	91	37.7	90	"	"	0	0	0	***
9	W.	M.	13.12.35	900	4.18	74	38.0	110	PP.	"	++	++	++	***
			23.12.35	800	—	—	37.8	100	"	"	++	++	++	***
			28.12.35	1,200	4.0	72	37.7	105	"	"	++	++	++	***
			3.1.36	650	—	—	37.8	105	HV.	"	++	++	++	***
			12.1.36	1,300	3.9	70	38.0	110	"	"	0	0	0	***
10	C.	M.	5.1.36	250	4.76	91	37.5	85	"	Yeast + liver	++	++	++	* Y.S.
			7.1.36	850	—	—	37.6	80	"	Yeast	++	++	++	* Y.S.
			10.1.36	650	—	—	37.5	85	"	"	++	++	++	***
			22.1.36	1,400	3.54	64	37.6	75	"	No	0	0	0	0
							below							
14	W.	M.	28.5.36	150	4.2	81	37.5	100	PP.	"	++	++	++	***
			29.5.36	170	—	—	37.5	90	"	"	++	++	++	***
			30.5.36	1,700	—	—	37.5	90	"	"	++	++	++	***
			31.5.36	275	—	—	37.5	80	"	"	++	++	++	lost
			1.6.36	350	—	—	37.5	85	"	"	++	++	++	***
			3.6.36	1,350	—	—	37.5	80	"	"	0	0	0	0

as ***; and more than 100 mg./litre as ****. The method has a high degree of accuracy when no yellowish-brown substance is present in the urine. As in most colorimetric methods the maximum error is between 2 and 5 per cent. depending on the intensity of the colour.

Most of the specimens which showed considerable concentrations of porphyrins were examined also by spectroscopic analysis with the Hartridge Reversion Spectroscope.

Results

The data of the pellagra cases in Cleveland are charted in Tables I and II. Of the pellagrous symptoms, only dermatitis, visible mucous membrane lesions, and diarrhoea have been tabulated, as the estimation of the subjective gastro-intestinal symptoms and the nervous disturbances is too difficult to lend itself to quantitative estimation. Delirium was, however, present in a number of the cases in the acute stage of the disease. The degree of increased porphyrin output is marked in asterisks, between the limits of * and **** as explained in the preceding paragraph.

Alcoholic cases: From Table I it is seen that of 14 patients with chronic alcoholism, 10 cases (Nos. 1, 3, 5, 6, 7, 8, 9, 10, 14, 15) showed increased porphyrinuria. Of these 10, one (No. 15) had no dermatitis at any time, while the remaining nine patients (Nos. 1, 3, 5, 6, 7, 8, 9, 10, 14) presented skin lesions of greater or less degree associated, with the exception of Case No. 14, with mucous membrane lesions. Of the nine cases with skin lesions associated with increased porphyrinuria eight (Nos. 1, 5, 6, 7, 8, 9, 10, 14) were followed to recovery, and a rough relation between improvement in symptoms and decrease in porphyrinuria was found to exist. In most of the cases not only the porphyrin concentration but also the total porphyrin output was considerably increased. In a few cases, however, the estimation of the porphyrin concentration was difficult owing to the presence of the yellowish-brown substance and that of the complete porphyrin output owing to the loss of urine through excessive diarrhoea. In one case (No. 8) the increased porphyrin output continued to some extent after the patient had become clinically well. However, in three of the cases (Nos. 6, 7, 15) followed, porphyrinuria subsided soon after admission although the symptoms were still quite definite.

Of 14 patients with active pellagra, four (Nos. 4, 11, 12, 13) showed no increased porphyrinuria at any time during their stay in the hospital. These four cases showed visible mucous membrane lesions of different severity, but the skin lesions were mild in three (Nos. 4, 11, 13) and absent altogether in one (No. 12). The latter case is of especial interest. The patient had been admitted earlier in the course of the study (as Case No. 8) and at that time showed an association of dermatitis with gastro-intestinal symptoms accompanied by increased porphyrinuria. When admitted a second time (as Case No. 12), while again showing mucous membrane lesions,

he exhibited no dermatitis, and at the time of the second admission there was no porphyrinuria present.

Of the eight cases with porphyrinuria and mucous membrane lesions which were followed through the course of the disease (Nos. 1, 5, 6, 7, 8, 9, 10, 15), the degree of porphyrinuria ran roughly parallel with the severity

TABLE III
(Healed Cases)

Case.	Race.	Sex.	Healed for period of.	Urine volume c.c./24 hrs.	RBC mill.	Hgb %	Diet.	General condition.	Porphyrins.
16	C.	M.	1 year	3,200	3.95	74	HV.	good	*
17	C.	M.	3 years	1,300	4.0	76	"	"	0

TABLE IV
(Controls: Healthy Subjects and Cases of Various Diseases)

Diagnosis.	Number of cases.	Whether receiving iron.	Porphyrins.
Healthy	17	No	0
	1	"	*
Various diseases (see page 307)	45	"	0
Hysteria	1	"	*
Anaemia secondary to bleeding	1	Yes	**
Macrocytic anaemia of unknown etiology	1	"	**
Idiopathic hypochromic anaemia	1	"	**
Monkeys: Nutritional macrocytic anaemia	2	No	0

TABLE V
(Healthy Controls receiving Liver Extract or Yeast)

Number of cases.	Medicaments received.	Diet.	Urine volume c.c./24 hrs.	Porphyrins.
5	5 c.c. liver extr. i-m. every day for 5 days.	HV.	Before liver: 1,000-2,800. 1 day after last dose: 900-3,100.	Before liver: 0. 1 day after last dose: 0.
5	75 g. brewer's yeast for 10 days.	HV.	Before yeast: 360-1,400. Last day of yeast: 800-1,400.	Before yeast: 0. Last day of yeast: 0.

of the symptoms. In some of the cases the increased porphyrinuria ceased before complete healing, and in others it had not yet stopped, although the other symptoms had remitted.

Non-alcoholic cases: In Case No. 2 no porphyrinuria was found in the presence of moderate dermatitis (cf. Table II). The additional case of secondary pellagra, not studied in detail clinically, showed a slightly but distinctly increased porphyrin excretion when first seen which disappeared within a week simultaneously with clinical remission.

Cured cases: Of the two cases (Nos. 16, 17) symptomatically free of pellagra for a period of one and three years, respectively, one (No. 16)

showed a slight degree of increased porphyrinuria, while the urine of the other was free from porphyrin (cf. Table III). In addition urine from one cured case seen in London was free from porphyrin.

Control observations: Of the 18 healthy individuals and 49 patients with various diseases (cf. Table IV), 17 of the former and 45 of the latter showed no increased porphyrinuria. One normal individual had a slightly increased porphyrin output as did one patient with hysteria. In addition three patients suffering from different types of anaemia and receiving iron medication showed a considerably increased porphyrinuria (**). Five control subjects receiving yeast over a period of ten days and five others receiving 5 c.c. of liver extract intramuscularly every day for five days (cf. Table V) showed no increased porphyrinuria. The two monkeys with mild nutritional macrocytic anaemia had no increased porphyrin output.

Nature of the porphyrins found: Spectroscopic analysis carried out in the majority of porphyrin-positive specimens, showed the porphyrin to be a coproporphyrin in each instance. The small amounts of urine available did not permit the preparation of porphyrin ester for further identification of the isomere series of the coproporphyrin (coproporphyrin I or III). Uroporphyrin was never found.

Due note has been made in Table I of the cell count, and haemoglobin content of the blood as well as the temperature and pulse. From this tabulation there appears to be no obvious relation between these and the porphyrin output.

Discussion

The finding of increased porphyrin excretion in our cases of alcoholic pellagra is in essential agreement with that obtained by Ellinger and Dojmi in cases of endemic pellagra. Among the alcoholic pellagrins, however, there seems to be a greater degree of variability in regard to the increased porphyrin output, but it must be mentioned that the alcoholic pellagrins presented symptoms somewhat different from the endemic group studied by Ellinger and Dojmi. In the endemic cases skin lesions were *always* present and were accompanied chiefly by mental confusion and spinal disturbances, while in the alcoholic group gastro-intestinal symptoms were much more pronounced and the skin lesions less severe.

As mentioned earlier in this paper, Ellinger and Dojmi (8) in their study of patients with endemic pellagra in Yugoslavia, found an increased porphyrin excretion in the urine which was greatest, in the majority of cases, in the early stages of the disease. In the present series most of the patients did not come under observation until they were severely ill and were not always seen in the early stages of the disease. It is therefore conceivable that this might be the explanation for the absence of increased porphyrin output in those of our cases which were negative. It is also possible that

the mildly increased porphyrinuria in one healed case (Table III, No. 16) may have been due to an impending relapse of pellagra.

The old controversy about the relation of the dermatitis to the exposure of the skin to light is well known. Spies (46) has shown, in certain instances at least, that pellagrous dermatitis is not due to sunlight exposure and he was unable to demonstrate uniformly any constant cause and effect relationship between exposure to sunlight and the development of pellagrous lesions. He does point out, however, that under certain conditions, sunlight may act as an irritant and precipitate cutaneous lesions of pellagra. This is at variance with reports by Ruffin and Smith (37) and Ellinger and Dojmi (7). The last two authors studied pellagrins in Yugoslavia during the spring of 1935 and observed a definite relation between development of skin lesions and exposure to sunlight. Thus, skin lesions while frequently present in peasant women of Roman Catholic faith were never found in Mohammedan women who form a large part of the population of that district. These Mohammedans consume a similar diet but are completely covered with clothing (even face and hands) when out of doors. Skin lesions were found on the feet only in people going barefoot. In this district the localization of the dermatitis varies at different seasons of the year, depending on the extent of the clothing.

The question of a possible relation of the skin lesions in pellagra to porphyrins in the circulation and consequently of the relation between skin lesions and exposure to light is, however, complicated by other factors. Kämmerer and Weisbecker (31) in their experiments on the light sensitization of mice by porphyrins found not only that the sensitizing effect of coproporphyrin was smaller than that of uroporphyrin, but they also observed that the animals exhibited a large individual difference in their sensitivity to light. Fischer and Zerweck (15) suggest that sometimes a protective effect may be produced by other pigments (brown pigment of the urine) or by the presence of the porphyrins as leuco-compounds. Also, two cases of human congenital porphyrinuria described by Micheli and Dominici (36) showed only very slight sensitivity to light, although in one of these the symptoms were caused by uroporphyrin. Sachs (38) has also described a case of uroporphyrinuria with little light sensitivity. Further complications are introduced through the observations of Schreus and Carrié (39) and of Gottron and Ellinger (22). These authors showed that in patients with congenital porphyrinuria porphyrins may produce not only sensitization to light but that they may also cause, quite independently of light exposure, skin lesions such as epidermolysis and the formation of bullae. Possibly the perineal location of skin lesions in pellagrins may be explained on such grounds. Furthermore, the light-sensitizing effect of porphyrins may be destroyed by their combination either with proteins (Shibuya (43), Hausmann and Haxthausen (29)) or with iron (Haurowitz (28)). Also, the effect of light is sometimes diminished by the reduction of the number of open capillaries in the skin observed in porphyrinuria by Schreus and Carrié (40)

and by Ellinger (5). This great individual variation in light sensitivity may well be responsible for a lack of skin symptoms even in cases with considerable porphyrinuria.

Relation to clinical signs of acute porphyrinuria. Of the clinical signs and symptoms seen in acute porphyrin intoxication (abdominal colic, mental confusion, marked constipation alternating frequently with bloody diarrhoea, polyneuritis, muscle pain, brown pigmentation of the skin, great sensitivity of any skin area to light, acute hallucinosis, anaemia, fever, tachycardia, and perspiration, cf. Kämmerer (32) and Vannotti (49), several are encountered in pellagra although usually in a milder form. The typical picture of acute toxic porphyrinuria as described by Mason, Courville, and Ziskind (35), accompanied by excretion of nearly black urine, has been observed by one of us (W. B.) in a patient with very severe pellagra which quickly remitted on appropriate treatment.

With regard to the non-pellagrins in our series who showed increased porphyrin output, we are unable to explain its occurrence in one healthy control and in one case of hysteria. Günther (24) has suggested a 'constitutional defect' in such individuals. In the three other control subjects who showed porphyrinuria it is seen that they were all suffering from macrocytic or microcytic anaemia and were all receiving iron medication. There were also, however, several cases of anaemia in our control subjects which exhibited no porphyrinuria. We are, therefore, inclined to attribute the increased porphyrin output to the iron therapy rather than to the anaemia. On the other hand, the not infrequent occurrence of porphyrinuria in various types of anaemia has been known for a long time. Duesberg (3) has attempted to clarify the question of the relation of porphyrinuria to the various types of anaemia, but the whole matter is still much confused.

In any attempt to explain the origin of the porphyrins found in the urine of pellagra patients it would be necessary to know the nature of the coproporphyrin present, whether it is coproporphyrin I or coproporphyrin III. In the absence of this knowledge any discussion must be speculative. We can eliminate two sources for the porphyrin: (a) the food, and (b) a faulty haemoglobin synthesis in which there might be a pathological persistence of the embryonic type of haemoglobin formation, as suggested by Fischer and Hilger (14) and later by Borst and Königsdörfer (2) for cases of congenital porphyrinuria. At least in the case of endemic pellagra in a maize-eating population the diet contains neither porphyrins nor substances which can be changed to porphyrins, and furthermore, pellagra is not a congenital disease. If the porphyrin found in pellagra should prove to be coproporphyrin I, which has been found in many of the pathological cases described as porphyrinuria, we have to consider the possibility of a complete new synthesis of the porphyrin, as suggested by Fischer and Duesberg (17). If, on the other hand, the porphyrin in pellagra is coproporphyrin III, we may assume a connexion with abnormal haemoglobin metabolism. Günther

(25) first suggested an abnormal change in the formation of bile or a defect in liver function as the cause of pathological porphyrin formation. Fischer and Duesberg (17) would explain the formation of porphyrins in the abnormal liver as follows: In the normal liver haemoglobin is changed to bilirubin, which according to Siedel and Fischer (44) belongs to the III series of isomeres and not to the IV as thought formerly. The bilirubin is then excreted as such into the bile-tract. In the functionally impaired liver bilirubin may be easily broken down into haematin and then to coproporphyrin III. This explanation seems a very plausible one.

Harbitz (26), Althausen (1), Thiel (47) and more recently Franke (18) have also pointed out the important role which liver insufficiency plays in the pathogenesis of porphyria. It is of interest to note that of the 11 cases of pellagra with a history of alcoholism which came to autopsy at Lakeside Hospital between September 1927 and September 1935, seven presented definite anatomical evidence of liver damage. It is not permissible to draw far-reaching conclusions from this fact in view of the well-known discrepancies between anatomical and functional liver changes. However, taking the various facts together it seems not too far fetched to suspect, in at least some of our cases, the presence of liver damage which in turn might be responsible for the presence of coproporphyrins in the circulation and in the urine.

Summary and Conclusions

1. The urinary output of porphyrin was studied in 14 cases of alcoholic pellagra, two cases of pellagra secondary to infectious disease of the gastrointestinal tract, and three cases of healed pellagra; also as controls in 18 healthy persons, 49 persons suffering from various diseases other than pellagra, two monkeys with mild nutritional macrocytic anaemia, and five normal subjects receiving yeast, and the same number receiving liver extract. Except for one case of secondary pellagra and some of the control cases, all cases were observed at Lakeside Hospital, Cleveland, U.S.A. Urine specimens were obtained at representative stages of the disease. No extremely mild attacks of pellagra are included in our series.

2. While the cases of endemic pellagra observed by Ellinger and Dojmi (8) in Yugoslavia had, without exception, in the beginning of the disease, a high porphyrin output usually disappearing early in remission but always when cured, the porphyrin output of the alcoholic cases in this study showed a greater variation. In most of the latter cases the porphyrin excretion bore a rough relationship to the intensity of the skin lesions and the mucous membrane lesions as the patients were watched in their progress toward recovery. On the other hand, among the patients showing no porphyria there were mild skin lesions in three cases and none in one case. The greater variability of porphyria in the alcoholic pellagrins may be in relation to the history of alcoholism.

3. Of 67 control subjects (healthy persons and those suffering from various diseases other than pellagra) only five showed an increased porphyrinuria, three of whom were receiving iron therapy.

4. The porphyrin present in the cases of pellagra was found to be a coproporphyrin.

5. A similarity is pointed out between the clinical symptoms of acute porphyrinuria and pellagra. One case of pellagra is described which exhibited all signs of an acute porphyrinuria.

6. A new colorimetric method is described for the quantitative estimation of ether-soluble porphyrins in small amounts of urine.

7. The origin of the porphyrins as well as their possible agency in the genesis of the skin lesions of pellagra is discussed. No further light was thrown on the relation between dermatitis and exposure to sunlight.

8. The necessity for a further study of a large series of cases of pellagra of different origin is evident.

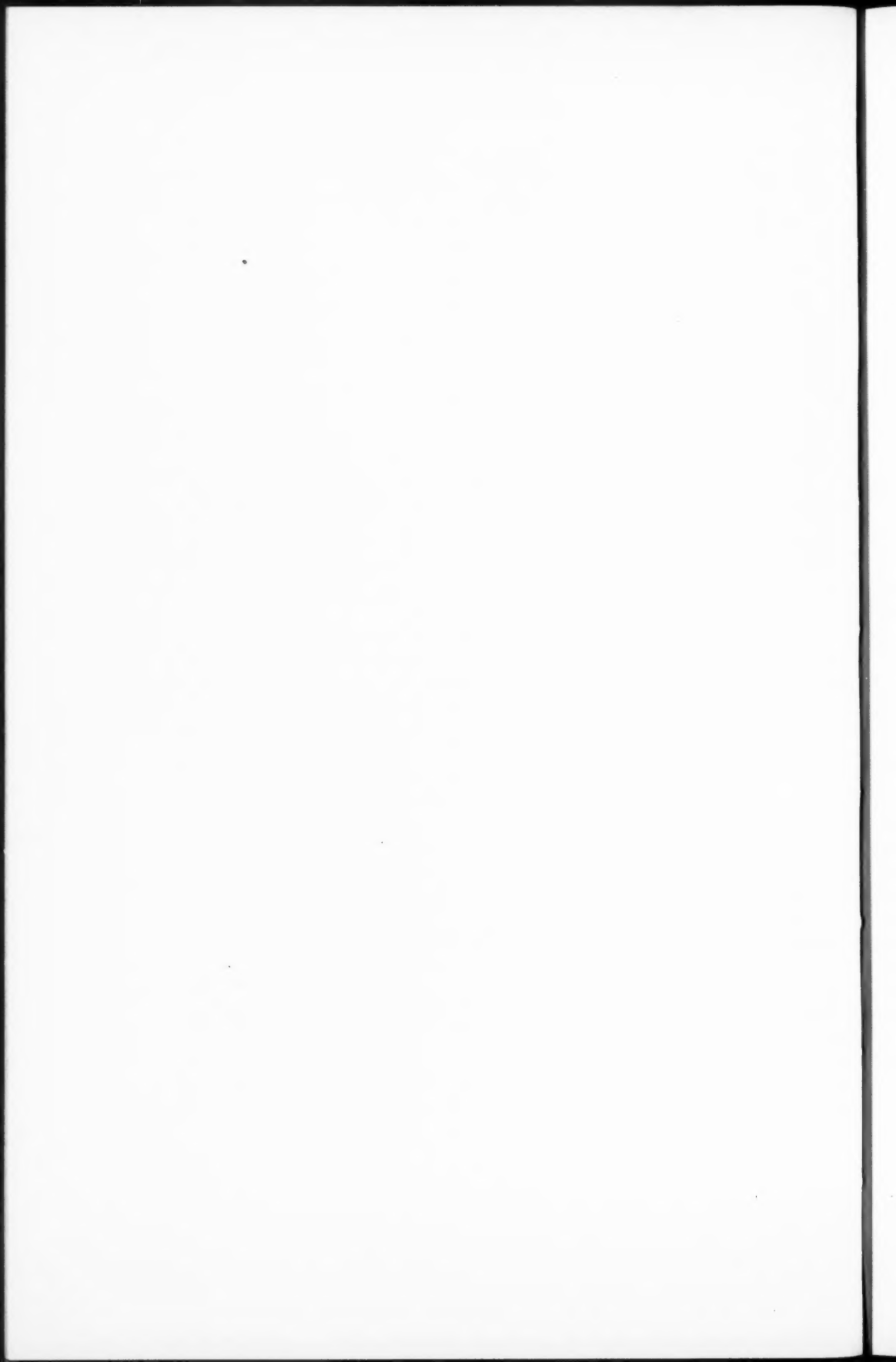
One of the authors (P. E.) takes this opportunity of expressing his indebtedness to the Society for the Protection of Science and Learning, London, for a Research Fellowship and to the Lister Institute of Preventive Medicine, London, for a personal grant and for its hospitality.

We wish to express our thanks to Dr. H. Chick for her continued interest in this work, to Dr. E. Guttmann, Prof. W. Mayer-Gross and Dr. W. Sargent, all of the Maudsley Hospital, London, and to Dr. S. Levy Simpson, London, who supported our work by providing for us the urine specimens and data relating to many of our control subjects and to the two London pellagrins, also to Dr. Lucy Wills, the London School of Hygiene and Tropical Medicine, London, for sending us the urine and the data of two monkeys suffering from mild nutritional macrocytic anaemia.

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THE ORGANIC MERCURIAL DIURETICS IN THE
TREATMENT OF CARDIAC OEDEMA¹

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Introduction

ALTHOUGH mercury appears in the Chinese medical literature so long ago as 2637 B.C., it was not used as a diuretic until Paracelsus in the sixteenth century applied it in the treatment of dropsy as well as for syphilis. During the following centuries it became a panacea for almost every complaint, so much so that its indiscriminate use led to the evolving of a new disease, the 'mercurial disease'. In 1810 Ferriar (35) admitted calomel as a diuretic, although he only mentions its use in one of his forty-seven cases of dropsy. Richard Bright (15, 16) does not seem to have regarded calomel as a diuretic, and decided against the use of mercury in the disease to which he was then giving his name. A few decades later, Pereira (88) was of the opinion that in dropsy 'mercurials may do either good or harm'. Stokes (109), on the other hand, states that: 'It happens again and again that the exhibition of mercury will, as by enchantment, remove the anasarca'. His indications for its use were (1) elderly patients—usually 50-70, (2) patients originally 'of healthy constitution and strong habit of body', (3) patients liable to gout, (4) patients subject to bronchitis, (5) where the liver is permanently enlarged. In 1866 Jendrassik (58) reported successful diuresis from calomel in six out of seven patients, while in 1889 Lépine (70) and Sée (107) drew attention to the risk of causing renal damage, although they favoured its employment. The papers of Cohnstein (23) in 1892 and Vejux-Tyrode and Nelson (113) in 1903 may be taken as typical examples of the literature then current on the subject.

Throughout this period the use of mercury as a diuretic adjuvant was appreciated to a certain extent, for it was a component of Guy's Pill; but it was not until recent years that its full value as a diuretic was fully appreciated, owing mainly to the discovery of a mercurial preparation which reduced to a minimum its toxic properties and enhanced its diuretic properties. It was in 1920 that Saxl (98), followed closely by Lange (67) and Kollert (65), showed the value of a new organic mercurial diuretic known by the trade name of novasurol. The use of this preparation as an anti-syphilitic remedy had previously been reported by Ziegler (117) in 1917.

Novasurol was soon followed by several similar preparations. In 1924

¹ Received March 23, 1937.

Bernheim (8) published a report on salyrgan, which, while being as potent a diuretic as novasurol, was less toxic. Three years later Mouquin, Giroux, and Schmidl (83) introduced neptal. The next step was the introduction in 1928 of a preparation containing an organic mercurial salt combined with theophyllin and known as novurit (57). These preparations must all be given intravenously or intramuscularly, but in 1934 the novurit suppository was produced containing the organic mercurial salt of novurit but not the theophyllin (30).

Chemistry. The organic mercurial diuretics, with one exception, being proprietary preparations, the following information is based upon either the literature issued by the manufacturers concerned or upon personal communications received from them.

Novasurol. Sodium oxymercuri-o-chlorphenyl-oxyacetate with diethylbarbituric acid.

Salyrgan. Sodium hydroxymereuric-methoxypropyl-carbamyl-phenoxyacetate. It occurs in the form of a fine crystalline powder containing not less than 37.6 per cent. of mercury in non-ionizable form. It is used as 10 per cent. aqueous solution, each c.c. of which contains gr. $\frac{1}{2}$ of mercury and 1.3 per cent. of dimethyl-xanthin. Since the present investigation was completed, 'salyrgan' has been modified, and the preparation now consists of 'a complex compound of mercury and sodium salicyl-allyl-amino-o-acetate in 5 per cent. theophyllin solution'.

Neptal. Hydroxymereuripropanolamide of o-carboxyphenoxyacetic acid. It is supplied in 1 c.c. ampoules, containing 0.092 grm. in sterile aqueous solution. Towards the end of the present investigation it was learned that theophyllin had been added to the preparation, so that the 'neptal' now available contains per c.c., 0.092 grm. of the mercurial salt plus 0.050 grm. of theophyllin. Most of the injections given during this investigation consisted of the original product.

Mersalyl. The sodium salt of salicyl-(γ -hydroxymereuri- β -methoxypropyl)-amide-O-acetic acid. It contains 38.5-40.5 per cent. of non-ionizable mercury. It is supplied for use in the form of a solution containing 10 per cent. of mersalyl and 5 per cent. of theophyllin. This preparation is included in the Addendum 1936 to the British Pharmacopœia (1).

Novurit. A sodium salt of trimethylcyclopentandicarboxylic acid allyl-amidmethoxymereurihydroxide with theophyllin. It is supplied in ampoules containing 0.1 g. of this preparation plus 0.05 grm. of theophyllin per c.c.

Novurit suppositories. These contain 0.5 grm. of the complex mercurial component of novurit without the theophyllin, in cocoa butter.

Pharmacology. A survey of the literature on this subject shows that there are two conflicting views on the mode of action of the mercurial diuretics—(1) that the diuresis is due to an extra-renal action in the tissues, (2) that the action is essentially on the kidneys themselves.

1. The supporters of the first of these hypotheses base their conclusions on changes in the blood and urine, which, they contend, are due to mobiliza-

tion of chloride and fluid from the tissues to the blood-stream. The assumption seems to be that the mercurial diuretics decrease the water-binding power of the tissues (103). The reported changes in the blood include a preliminary fall in the plasma proteins (101, 102, 12, 22, 66), and increased blood volume (34), and a reduction in the plasma chlorides in the early stages, followed by a rise at a later stage (102). Other supporters of this theory base their findings on changes in the rate of absorption of normal saline or water injected subcutaneously following the injection of the mercurial diuretics (112, 76, 31, 13). The fallacy in all such work is the attempt to draw conclusions as to the mode of action of diuretics from changes in isolated constituents of the blood or urine. As Marshall and Kolls (80) have shown, the effects of diuresis are the same as those obtained after denervation of the kidneys, i.e. the total solids, total nitrogen, urea, and chlorides in the urine are increased. The percentage of chlorides in diuretic urine may even rise, while other constituents are decreased in percentage, at least during the height of diuresis. Blumgart and his co-workers (10, 11) also concluded, from studies of blood and urine chemistry, that the diuresis with the mercurial diuretics was not due to changes in the concentration of blood constituents.

2. More convincing proof has been advanced in favour of a renal action for these diuretics. Govaerts (46, 47), by means of transplanting kidneys into the neck, has found that diuresis was only obtained from the kidneys which had been subjected to the effect of novasurol. Bartram (5) injected salyrgan directly into the left renal artery of dogs and collected the urine at half-hour intervals from each ureter. He found that, with small doses of salyrgan, diuresis only ensued in the injected kidney. Several investigators, using the creatinine-clearance method of Rehberg, have concluded that salyrgan causes a marked diminution in tubular absorption with little, if any, increase in glomerular filtration (55, 54, 106, 104, 105, 21).

The theory of a renal action is in agreement with the well-established fact that one of the major actions of mercury is upon the tubules of the kidney (86, 78, 79, 52, 56), and with Richards' (94) observation that in the frog's kidney mercury perchloride abolishes the power of active reabsorption by the tubules.

On the evidence available, of which the above is a bare summary, the conclusion follows that, so far as our present knowledge goes, the diuresis of the organic mercurial diuretics is due to the mercury component acting on the tubules of the kidneys and diminishing their power of absorption.

Should such be their mode of action, the question would naturally be raised as to the possibility of combining them with the xanthine group of drugs which are known to act mainly through increasing glomerular filtration. Such a combination has been mentioned by isolated workers since the introduction of novasurol (19, 72, 20), but it was not until 1928 that Issekutz and Vegh (57) finally reported their results with a preparation containing both a mercurial salt and theophyllin. This preparation known as novurit,

they claimed, produced a greater diuresis than an organic mercurial diuretic without theophyllin. Since then Herrmann and his co-workers (55, 54, 106), giving a xanthine derivative and an organic mercurial preparation simultaneously to patients, have confirmed the enhanced diuresis that may be obtained with this combination, compared with either group separately.

Methods of administration and dosage. For practical purposes the three methods of administration that need be considered are intramuscular, intravenous, and as a suppository. For the sake of completeness, however, the other methods that have been used will be briefly summarized.

By mouth. Fleckseder (38) gave salyrgan by mouth, combined with ammonium chloride, but with very moderate success.

Intrapleural. It has been recommended that in the presence of pleural effusions, diuresis may be obtained by removing part of the fluid by paracentesis and then injecting salyrgan into the cavity (14).

Intraperitoneal. More successful results have been obtained by intraperitoneal injections in selected cases, particularly of ascites. Large doses should be given, 5-6 c.c. (53, 28). Thus Hartl (53) reports a diuresis of 280 ounces on the first day following intraperitoneal injection of 6 c.c. of salyrgan, with 230 ounces on the second and 200 ounces on the third day. This worker considers that the diuresis thus obtained is four times greater than with intravenous administration, and is due to the slower absorption resulting in a more prolonged action on the kidneys. Inadequate dosage may explain the failure of Rowntree and Barrier (96) to obtain diuresis in their case of ascites.

Subcutaneous. In view of the undoubted irritation and sloughing that occurs with accidental leakage into the subcutaneous tissues during intravenous medication, there is no justification for using the above route. Yet apparently it has been administered by this route without provoking sufficient signs to induce workers to refer to them (73, 9).

Intramuscular. In many clinics, this is considered to be the method of choice, particularly with neptal. With this preparation it is claimed that, given intramuscularly, a second diuresis is obtained several days after the diuresis obtained during the first twenty-four hours. On the other hand, several workers report more pain by this route than intravenously (42, 71). The advantages of this route are that it avoids sclerosis of the veins and is accompanied by less risk of subcutaneous infiltration. Of their efficacy by this route, there can be no doubt, as is demonstrated by the case in which a diuresis of 481 ounces was obtained following upon the intramuscular injection of neptal (91). Dosage is the same as for intravenous administration.

Intravenous. This is undoubtedly the most universal and the most successful method of administration. The objections to it are those that apply to any form of intravenous therapy, and in addition there is the risk of subcutaneous leakage and ultimate sclerosis of the vein should repeated injections be required. To minimize the risks arising from possible leakage, it has been recommended that the drug should be given diluted to 10 c.c.

with normal saline (6, 116). In addition many workers recommend that an initial dose of 0.5 c.c. should be given to test the sensitivity of the patient to mercury. In the case of all the preparations, the dosage both intravenously and intramuscularly is 1-2 c.c. of the solution supplied by the manufacturers. Injections should not be repeated oftener than every third day, i.e. with two clear days between injections.

Suppository. The only suppository, concerning which there is personal experience or reference by other workers, is the novurit suppository. This is given, at intervals of not less than three days, as indicated in each individual case. Premedication consists of an aperient two nights before or an enema a few hours before the suppository is given.

Acid-producing salts as an adjuvant to the organic mercurial diuretics. The principal acid-producing salts to be used as diuretics are ammonium chloride, calcium chloride, and ammonium nitrate. In practice calcium chloride has been largely discarded on account of its tendency to cause gastro-intestinal disturbances. Of the other two, ammonium nitrate, which has been recommended by Keith and his colleagues (64, 63) has the disadvantage of occasionally causing methaemoglobinaemia (33, 110), and of not being so certain in its action as ammonium chloride. The latter's main disadvantage is its unpleasant taste, but this may be overcome by giving it as a tablet or capsule.

The action of these salts has been investigated by numerous workers, including Haldane, Gamble, and Peters (49, 3, 50, 51, 44, 43, 90, 89). Their action is to produce an acidosis which disturbs the Donnan equilibrium and so alters osmotic pressure values in the body fluids.

It is almost unanimous that these salts, in combination with the organic mercurial diuretics, produce an increased diuresis as compared with the mercurial diuretics alone, though there is a difference of opinion on the optimum dosage. On the one hand is the practice of giving the salt for long periods, on the other the practice of merely giving it for a short period immediately before the mercurial diuretic. The latter course is advocated by Saxl and Erbsbacher (100) and Ethridge, Myers, and Fulton (32), who recommend that the acidifying salt should be given for two days preceding, and on the day of, the mercurial injection. Bennett (7) gives ammonium chloride on the two days preceding the administration of salyrgan. Dennig, Dill, and Talbot (27) found that, with ammonium chloride, the degree of acidity was more marked on the second and third days than subsequently.

The majority of workers have advocated large doses, up to 10 gm. per diem. In a later section of this paper, figures will be given relating to this question, but it may be stated at this stage that there is no proof that there is any intrinsic advantage in such extreme doses, especially as they can produce unpleasant symptoms. The optimum dosage probably varies from individual to individual, and is largely dependent upon the relative values of the various factors which contribute to the acid-base equilibrium of the body at the particular time when the salt is given.

Indications and contra-indications. For brevity, these two points will be discussed together.

Cardiac oedema. There is almost complete unanimity (among all workers in all countries) that this is the indication for the organic mercurial diuretics. In elderly patients, however, diuresis may not be obtained, as has been pointed out by Lyon (77), among others. Indeed, Goldring (45) maintains that these diuretics should be used with caution in elderly people, while Saxl and Heilig (101) recommend caution in emaciated persons. In the failure associated with acute coronary thrombosis, Fishberg (37) claims that they are 'strongly contra-indicated', though this is not the experience of Master and Dack (81), who recommend salyrgan and avoid digitalis under such conditions.

Cardiac failure without oedema. Several workers have recommended the use of the mercurial diuretics in heart failure where dyspnoea is the presenting symptom and there is little or no oedema (40, 71). Friedman and his co-workers suggested that this might be due to salyrgan reducing oedema in the heart muscle (40).

Renal oedema. Opinion is divided as to the advisability of using the mercurial diuretics in renal disease. Most workers agree that they should be used in nephrosis or the nephrotic syndrome (39, 61, 7, 37, 4), and there is general unanimity that they should not be used in acute nephritis (6, 114, 116, 92). Opinion is divided as to their use in other types of nephritis. Oerting (84) states that renal oedema and nephritis are absolute contra-indications, and Rathery and Maximin (92) would exclude practically all such cases, while Dorner (28) and Dwyer (29) report success in cases of 'tubular nephritis'. Perhaps the position is best summarized by stating that in acute nephritis the mercurial diuretics are definitely contra-indicated, in nephrosis or the nephrotic syndrome they are indicated, while in subacute or chronic nephritis with hypertension and impaired renal function, they should be used with great caution. Fishberg (37), for instance, does not give them if patients are unable to concentrate the urine to a specific gravity of at least 1015; and Lécene and others (69) recommend that the decision should be made according to tests of renal function and not according to the blood urea.

Ascites. The mercurial diuretics should be tried in ascites, no matter what the cause may be (101, 103, 4), though the results are not so satisfactory in non-cardiac patients (75, 72). Rowntree, Keith, and Barrier (97) have reported successful results in 17 out of 20 patients with ascites and hepatic disease. Fulton (41), however, in a series of 37 patients obtained unsatisfactory results, although he agrees that the mercurial diuretics should always be tried. In severe hepatic degeneration, considerable caution should be used (116).

Among the contra-indications should be included colitis, enteritis, or diarrhoea (6, 108, 114, 116) and haematuria (6, 116). Foster (39), indeed, goes so far as to say that haematuria is 'the sole contra-indication'.

Haemophilia or the haemorrhagic diathesis may also be regarded as a contra-indication (83), and considerable caution should be shown where there is pyrexia (83).

The position may thus be summarized:

Indications. (1) Cardiac oedema, with caution in the presence of fever and in the elderly; (2) cardiac failure without oedema; (3) renal oedema, provided the renal efficiency is not unduly impaired and haematuria is absent; (4) ascites.

Contra-indications. (1) Haematuria; (2) severely impaired renal efficiency; (3) colitis, enteritis, or diarrhoea; (4) fever; (5) advanced cachexia; (6) haemorrhagic diathesis. In addition, mercurial suppositories should not be used in patients with proctitis or inflamed haemorrhoids, though uncomplicated haemorrhoids are not a contra-indication.

Toxic effects. The mercurial diuretics are for all practical purposes safe preparations, used in correct dosage and in suitable patients. Thus Bernheim (8) has reported no toxic effects in 1,000 injections of salyrgan, and Grossman (48) found none in 10,000 injections. Other workers who report an absence of toxic signs include Lian and Puech (73), Barker and O'Hare (4), and Crawford and McDaniel (24). On the other hand, certain toxic effects do occur. In 618 patients Hug (56a) found 16 in which salyrgan had to be stopped on account of toxic signs. Experimentally, it has been repeatedly shown that the brunt of the action of these preparations falls on the kidneys, causing necrosis of the tubules (60, 68, 62, 59, 18).

Necropsy statistics show the true incidence of renal damage from the mercurials to be so low as to be almost insignificant. Thus Tarr and Jacobson (111), among 30 necropsies on patients who had had salyrgan, found only one with a renal lesion suggestive of mercurial intoxication, while Maxwell, Scott, and Harvey (82), as a result of post-mortem examination of 21 cases of congestive heart failure who had had salyrgan, report that 'changes in the kidneys from patients who had had mercurial diuretics are in no way different from those commonly seen in patients dying of congestive cardiac failure without the use of mercury'. One of their cases had received 240 c.c. of salyrgan. Kollert (65) also reports similar results in necropsies in syphilitics who had received novasurol. Schwab, Herrmann, and Stone (106) refer, without giving details, to two cases of anuria following prolonged use of salyrgan, in which extensive tubular damage was found *post mortem*. Rosenthal (95) refers to a patient who died after two doses of salyrgan, and tubular necrosis was found at necropsy. He concludes that the patient must have been particularly sensitive to mercury. Saxl (99) doubts whether the three deaths following novasurol reported by Redlich (93) were really due to novasurol. The sudden death reported by Wolf and Bongiorno (115) was probably due to anaphylaxis, for this patient died as the needle was being withdrawn after the sixth injection of salyrgan.

The toxic effects of the mercurial diuretics include stomatitis, diarrhoea, vomiting, haematuria, malaise, rigors, and purpuric eruptions.

There is a small group, in which toxic effects are due to faulty technique, either leakage into the subcutaneous tissues during intravenous or intramuscular medication, or faulty intramuscular administration. Thus Tarr and Jacobson (111) in their series of 30 necropsies, found one example of wrist-drop and two of foot-drop due to faulty intramuscular technique. Agnew (2) reports a slough due to an intramuscular injection which was not made deeply enough, and Binger and Keith (9) found local necrosis in three cases receiving salyrgan intramuscularly. It is interesting in this connexion to note that the combination of theophyllin with a mercurial diuretic seems to decrease the local toxic action both in animals and man (26). It cannot be denied that slighter degrees of local irritation, pain, and redness do occasionally occur from oozing into the tissues, even when care has been taken.

Clinical Investigation

The aims of this investigation may be summarized as follows: (1) An evaluation of the therapeutic effects of the organic mercurial diuretics in cardiac oedema. (2) An enquiry into the relative merits of the several members of this group, comprising salyrgan, novurit, mersalyl, neptal, and novurit suppositories. One of the xanthine group, deriphyllin, was also used in a few patients. (3) A study of the combined effects of an acid-forming salt (ammonium chloride) and the organic mercurial diuretics. (4) A study of the effects of digitalis or strophanthin in combination with the organic mercurial diuretics.

The present study concerns 66 patients, 61 of whom were suffering from congestive heart failure. In addition there were three patients with chronic bronchitis without congestive heart failure, one patient with cirrhosis of the liver with ascites, and one with malignant disease of the liver with ascites. (Table I).

The patients with congestive heart failure represent those admitted to the London Hospital under the care of Dr. John Parkinson between June 1935 and November 1936. They were not selected in any way, and so they include every grade of heart failure, from those with only a trace of oedema in the legs to those with gross anasarca. Table II shows the distribution according to the amount of oedema, while Table III shows the age distribution. The apparent discrepancy in the total number of cases in Table II compared with Table I is due to re-admissions being treated as separate cases for the purposes of Table II. Of those with heart failure, 28 had normal rhythm, 32 had auricular fibrillation, and one patient who had normal rhythm on admission, developed auricular fibrillation while in hospital. Six patients were admitted to hospital twice during the course of the investigation.

All patients were kept strictly in bed, and, apart from the organic mercurial diuretics, ammonium chloride, digitalis, and strophanthin, drug therapy was reduced to a minimum. Morphine was administered when

necessary, and patients with chronic bronchitis, whether with or without heart failure, sometimes received a simple expectorant mixture. Fluid intake was restricted, the amount allowed varying in individual cases from 20 to 40 oz. (570-1,140 c.c.) in the twenty-four hours. The diet was poor in sodium chloride, but not strictly salt-free.

TABLE I

Classification According to Diagnosis

Total	66 cases
Congestive heart failure	61 "
Chronic bronchitis without failure	3 "
Cirrhosis of liver with ascites	1 case
Carcinoma of liver with ascites	1 "
Rheumatic heart disease	27 cases
Hypertensive and arteriosclerotic heart disease	31 "
Syphilitic heart disease	1 case
Unclassified heart failure	2 cases

TABLE II

Classification of Patients with Congestive Heart Failure According to Amount of Oedema

Degree of oedema	±	+	++	+++	++++
Number of cases	6	17	14	21	9
± =	Trace of oedema at ankles				
+	Pitting oedema of legs				
++ =	Pitting oedema of legs + enlargement of liver				
+++ =	Pitting oedema of legs + enlargement of liver + hydrothorax				
++++ =	Anasarca				

TABLE III

Age Distribution

Age group (years)	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Number of cases	2	6	5	12	17	21	3

Unless the patient's condition precluded the withholding of active treatment, no medication was administered until the patient had been under observation for several days, and the urinary output had been stabilized. Occasionally the patient was so seriously ill that either digitalis, strophanthin, or one of the organic mercurial diuretics had to be given either on admission or before this preliminary control period had been completed.

The subsequent course of therapy was varied from case to case; (1) Novurit suppository preceded by enema a few hours before. With or without previous administration of ammonium chloride. (2) Novurit suppository. Aperient two nights before. With or without previous administration of ammonium chloride. (3) Novurit intravenously. With or without previous administration of ammonium chloride. (4) Salyrgan intravenously. With or without previous administration of ammonium chloride. (5) Mersalyl intravenously. With or without previous administration of ammonium

chloride. (6) Neptal intravenously or intramuscularly. With or without previous administration of ammonium chloride.

In view of the well-known fact that the amount of diuresis is partly dependent upon the extent of the oedema, the sequence in which the various preparations were administered was varied from case to case, so that no one preparation was given exclusively either to patients with gross oedema or to those with only slight oedema.

TABLE IV

Showing Number of Injections and Suppositories Administered

Novurit	53 injections
Salyrgan	71 "
Neptal	18 "
Mersalyl	11 "
Novurit suppositories	208
Deriphyllin	7 injections
Deriphyllin suppositories	6
Normal saline	1 injection

Novurit, salyrgan, and mersalyl were invariably given intravenously in doses of 2 c.c., undiluted, into one or other antecubital vein. Neptal was given either intravenously into an antecubital vein or intramuscularly in the gluteal region in doses of 1 or 2 c.c. Deriphyllin was given intravenously into the antecubital vein in doses of 2 c.c. In using the suppositories only one of the novurit suppositories was given in the twenty-four hours, but two deriphyllin suppositories. The preparation was always given in the morning and the second three to four hours later. Table IV shows the total number of injections and suppositories administered during the investigation.

The interval between the administration of any of these preparations varied considerably, but was never less than two clear days.

Ammonium chloride was given in very varying amounts in order to find the optimum dose. Except in three patients, it was never given for more than four days preceding the mercurial salt, nor continued beyond the day of administration of the latter. The daily dose varied from gr. 30 (2 grm.) to gr. 120 (8 grm.) and the maximum amount given in combination with any one dose of a mercurial salt was gr. 300 (20 grm.). Of the three patients mentioned, two received it continuously, the daily dose being gr. 60 (4 grm.) and gr. 80 (5.3 grm.) respectively, while in the case of the third, gr. 75 (5 grm.) was given daily for four days, the mercurial salt being administered on the third day.

A drawback in the use of ammonium chloride is the difficulty in disguising its salty taste, and sometimes this constitutes a very real difficulty. Early in this investigation it was prescribed with liquid extract of liquorice, as recommended in the British Pharmaceutical Codex (17), but the disguise is thin. It was then decided to administer the salt in tablet form, and the result was wholly successful. The tablets contain gr. 10 (0.66 grm.) and keep well; they are of reasonable size and acceptable to the patient. Specimens which have been kept in an ordinary stoppered bottle for one year show no signs of

deterioration. Prior to the use of tablets, an attempt was made to give the salt in capsules, but these proved rather large for comfortable swallowing.

Of the patients with congestive heart failure, 33 had digitalis or strophanthin at some time during their stay in hospital, while the remaining 28 had none. As a rule digitalis was given, either as the tincture or as the leaf. The dosage never exceeded $\text{m} 45$ (2.6 c.c.) of the tincture or gr. 3 (0.2 grm.) of the leaf daily. In five cases strophanthin was given, gr. 1/100-gr. 1/50 (0.00065-0.0013 grm.), intravenously.

TABLE V

Showing Average Twenty-four Hours Diuresis Obtained with Various Organic Mercurial Diuretics and the Effect of Ammonium Chloride and Digitalis on such Diuresis

Diuretic.	All cases.			With digitalis.			Without digitalis.		
	With ammon. chlor.	Without ammon. chlor.	Total.	With ammon. chlor.	Without ammon. chlor.	Total.	With ammon. chlor.	Without ammon. chlor.	Total.
	oz.	oz.	oz.	oz.	oz.	oz.	oz.	oz.	oz.
Novurit	87.2	70.7	82.8	82.6	66.6	79	88.2	71.7	83.3
Novurit suppository									
Novurit	117	78.6	105.4	109.8	56.8	90.5	121.4	100.4	115.9
Salyrgan	102	81.1	93.7	99.8	93.3	96.7	102.6	76.2	92.8
Mersalyl	98.2	126	100.7	87	—	87	101	126	103.8
Average	94.8	75.4	89.1	91.3	71.6	85.4	95.7	76.8	90.3
Diuresis in c.c.	2,690	2,140	2,530	2,590	2,030	2,430	2,720	2,180	2,570

TABLE VI

Showing Average Twenty-four Hours Diuresis Obtained with Novurit Suppositories and the Effect of Ammonium Chloride and Premedication in such Cases

Total.	With A. C.	Without A. C.	With E.	With A.	Without E. or A.	A. C. + E.	A. C. + A.	A. C. No E. or A.	E. No A. C.	A. No A. C.	Without A. C., E. or A.
oz.	oz.	oz.	oz.	oz.	oz.	oz.	oz.	oz.	oz.	oz.	oz.
82.8	87.2	70.7	85.4	86	68.1	86.2	88.7	76.7	84.1	57.1	60.8
c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.	c.c.
2,350	2,480	2,010	2,420	2,440	1,930	2,450	2,520	2,180	2,390	1,620	1,730

Number of Suppositories.

208	153	55	66	107	35	40	98	16	26	9	19
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A. C. = Ammonium chloride.

E. = Enema.

A. = Aperient.

Results

From lack of space it has not been possible to reproduce the detailed results, so the averages have been arranged in Tables V and VI. Table V shows that the average twenty-four hours urinary output for novurit suppository was 83 oz. (2,360 c.c.), compared with 105 oz. (3,000 c.c.) for novurit, 94 oz. (2,670 c.c.) for salyrgan, and 101 oz. (2,860 c.c.) for mersalyl. The comparable figure for neptal given intravenously was 94 oz. (2,670 c.c.). The maximum individual twenty-four hours urinary output (for each) was 236 oz. (6,700 c.c.) for novurit suppositories, 189 oz. (5,370 c.c.) for

novurit, 211 oz. (6,000 c.c.) for salyrgan, 198 oz. (5,630 c.c.) for mersalyl, and 140 oz. (4,000 c.c.) for neptal.

It is seen that the intravenous preparations had a larger average diuresis than the novurit suppositories. To give a more concise comparison, the whole of the intravenous results have been averaged, showing that the average twenty-four hours urinary output per intravenous injection was 99 oz. (2,810 c.c.) compared with 83 oz. (2,360 c.c.) per suppository.

Table VI relates to the preparation of the rectum for the suppositories. Either an aperient, in this series usually cascara, was given two nights before the suppository, or else an enema was given a few hours before. There was little to choose between the two methods, so far as diuresis is concerned, the average for the aperient cases being 86 oz. (2,440 c.c.) compared with 85 oz. (2,410 c.c.) for the enema cases. On the other hand, the cases which received neither aperient nor enema had only an average of 68 oz. (1,930 c.c.).

Ammonium chloride as an adjuvant to the mercurial preparations, was used at some time or other in almost every case, and an analysis of the results is seen in Tables V and VI. Excluding the few observations on mersalyl and neptal, it is clear that for novurit suppositories, novurit and salyrgan, the average diuresis when ammonium chloride is combined with them was considerably higher than when it was omitted. The results are for the novurit suppositories 87 oz. (2,440 c.c.) with ammonium chloride, 71 oz. (2,020 c.c.) without; for novurit 117 (3,320 c.c.) and 79 oz. (2,240 c.c.) respectively; and for salyrgan 102 (2,900 c.c.) and 81 oz. (2,300 c.c.).

An attempt has been made to establish the optimum dose of ammonium chloride when used in combination with the mercurial diuretics. Twenty-seven different methods of dosage were used, varying from a single dose of gr. 30 (2 grm.) for one day to gr. 80 (5.3 grm.) daily throughout the entire period of observation. In view of the number of different doses used, it is inevitable that in a series of 65 patients, the available figures should be small. Yet the results are of some value, for they suggest that there is little advantage in continuous administration of the salt, e.g., the average urinary output for the 19 observations with gr. 80 (5.3 grm.) of ammonium chloride was 102 oz. (2,900 c.c.) compared with 119 oz. (3,580 c.c.) for the 11 observations with gr. 80 (5.3 grm.) given daily throughout the period of observation. The maximum average output in this series was 123 oz. (3,490 c.c.) obtained with gr. 90 (6 grm.) of ammonium chloride on the day preceding, and gr. 120 (8 grm.) on the day of the administration of a mercurial salt.

The diuretic effect of ammonium chloride alone is inconsiderable. In the 62 cases, where the figures are complete, the average twenty-four hours urinary output per daily dose of this salt was 39 oz. (1,110 c.c.) compared with an 'average normal output' of 35 oz. (990 c.c.). For the purposes of this paper the 'average normal output' per patient has been defined as the average twenty-four hours urinary output for the patient's entire stay in hospital, excluding (a) the days upon which ammonium chloride was

given, (b) the days upon which a mercurial diuretic was given, (c) the second twenty-four hours after each administration of a mercurial diuretic.

In the entire series the diuresis with ammonium chloride alone exceeded 100 oz. (2,840 c.c.) on four occasions as follows: (1) In a patient with auricular fibrillation and heart failure without valvular lesion when gr. 120 (8 grm.) of ammonium chloride was given on the first day and gr. 90 (6 grm.) on the second. The diuresis on the second day was 112 oz. (3,180 c.c.). (2) In a patient with aortic stenosis, bundle-branch block, normal rhythm and heart failure, receiving the same dosage of ammonium chloride as (1). The diuresis occurred again on the second day and amounted to 107 oz. (3,040 c.c.). (3) In a case of mitral stenosis, auricular fibrillation, and heart failure who had received gr. 60 (4 grm.) on two successive days. The diuresis of 107 oz. (3,040 c.c.) occurred on the first day. (4) In a case of hypertension, auricular fibrillation, and heart failure who received gr. 80 (5.3 grm.) for a day with a diuresis of 126 oz. (3,580 c.c.). The 'average normal output', as already defined, for these cases was respectively 36 oz. (1,020 c.c.), 36 oz. (1,020 c.c.), 47 oz. (1,340 c.c.), and 36 oz. (1,020 c.c.).

Digitalis was administered at one time or other to 33 patients with congestive heart failure, while the remaining 28 in this group received none. Observations on the effect of the mercurial diuretics both with and without digitalis in the same patient are available in 19 cases of congestive heart failure.

Table V shows the unexpected result that in the case of each preparation, with the exception of salyrgan, the average diuresis happens to be greater when digitalis is not given than when it is given. This applied whether ammonium chloride had been given at the same time or not. Attention must, however, be drawn to the fact that the number of administrations of mercurial diuretics is much greater in the group which had not received digitalis. In an attempt to elucidate this point, the following analyses have been made. The average twenty-four hours diuresis per dose of novurit suppository, novurit, and salyrgan has been obtained for all cases of congestive heart failure with normal rhythm and all cases of failure with auricular fibrillation (Table VII). In both these groups the diuresis was found to be greater in the non-digitalized cases. The exception to this rule is that digitalis seemed to favour diuresis in the patients who received salyrgan. This Table also shows that in the fibrillation group the average diuresis for all observations is greater in the non-digitalis group than in the digitalis group, while in the cases of normal rhythm there is practically no difference. Combining the cases with normal rhythm and those with auricular fibrillation, the average diuresis for the non-digitalis group is 93 oz. (2,640 c.c.) (227 observations), compared with 89 oz. (2,530 c.c.) for the digitalis group (89 observations). In 19 patients who had periods both with and without digitalis the average diuresis for the mercurial diuretics combined with digitalis was 89 oz. (2,530 c.c.) compared with 86 oz. (2,440 c.c.) for the non-digitalis observations. In the former group

66 per cent. of the observations were accompanied with ammonium chloride, and the comparable figure for the latter group was 70 per cent. These findings show that the administration of digitalis had surprisingly little, if any, effect on the diuresis produced by the mercurial diuretics in congestive heart failure.

TABLE VII

Showing Average Twenty-four Hours Urinary Excretion Following the Administration of the Organic Mercurial Diuretics (a) with Digitalis, (b) without Digitalis, in Cases of Congestive Heart Failure, (i) with Normal Rhythm, (ii) with Auricular Fibrillation

Diuretic.	Normal rhythm.			Auricular fibrillation.		
	With digitalis.	Without digitalis.	Total.	With digitalis.	Without digitalis.	Total.
	oz.	oz.	oz.	oz.	oz.	oz.
Novurit suppository	80.8	83.1	82.9	76.7	94.2	85.7
Novurit	103	116.6	115	84.5	125.4	93.8
Salyrgan	104.2	96.2	97.8	152.3	91.3	110.7
Average diuresis	93.4	90.9	91.2	86.9	96	91.4
In c.c.	2,650	2,580	2,590	2,470	2,730	2,600
Total number of observations	22	159	181	65	63	128

TABLE VIII

Showing the Average Daily Urinary Excretion of the Three Days Following the Administration of the Organic Mercurial Diuretics

Diuretic.	'Average normal output'	First day.	Second day.	Third day.
	oz.	oz.	oz.	oz.
Novurit suppository	34 (64)	84 (204)	37 (185)	33 (107)
Novurit	32 (39)	105 (53)	40 (47)	29 (32)
Salyrgan	34 (46)	94 (67)	35 (57)	30 (35)
Mersalyl	33 (9)	101 (11)	44 (7)	42 (6)
Neptal	39 (10)	85 (18)	32 (15)	31 (13)
Total average	35 (68)	90 (353)	41 (311)	32 (193)
In c.c.	990	2,560	1,160	910

The figures in brackets represent the number of observations upon which each average is based.

Intramuscular medication. Except in the case of neptal, which is recommended by the manufacturers for intramuscular use, all patients received these diuretics either intravenously or as a suppository. Of the eighteen injections of neptal, nine were given intravenously (six of 1 c.c. and three of 2 c.c.) and nine intramuscularly (five of 1 c.c. and four of 2 c.c.). The average twenty-four hours diuresis per injection was 94 oz. (2,670 c.c.) for the intravenous group and 77 oz. (2,190 c.c.) for the intramuscular group.

Duration of diuresis. Table VIII shows that the diuresis is largely spent in twenty-four hours. Thus the average diuresis for all administrations is 41 oz. (1,160 c.c.) on the second day and 32 oz. (910 c.c.) on the third.

It is interesting to see that the figure for the second is above, and the figure for the third day only slightly less than, the average diuresis for the days on which diuretics were not administered—35 oz. (990 c.c.). The apparent discrepancy in the figures in this Table compared with the figures for the series given earlier in the paper is due to the omission of a few patients where it was not possible to calculate the average diuresis for the non-diuretic days, while the patients observed twice in hospital have been regarded as two distinct patients.

Toxic effects. No serious toxic effects due to the mercurial diuretics were ever observed, yet because of its importance, it is proposed to give a full account of all such occurrences, many of which could be more correctly classified as 'discomforts' rather than 'toxic effects'. In two instances, some leakage into the subcutaneous tissues occurred during intravenous administration of novurit. In one, the leakage was due to sclerosis of the veins following upon frequent intravenous injection; the arm became very painful and swollen for forty-eight hours and morphia was required once to relieve the pain. Subsequent recovery was complete. In the other, the pain was not so severe and there was no local rise of temperature. On only two occasions did rigors occur, once, one hour after the administration of a novurit suppository, the temperature rising to 100.9° F.; by the evening the temperature was 98° F., and at no time was there any tenesmus or local irritation. In the other patient the rigor occurred six hours after the intravenous injection of novurit (2 c.c.), lasted for ten minutes, and the temperature reached 101.8° F. In two patients pyrexia was present in the evening of the day on which diuretics were given. In one, the evening temperature was 99.6° F., and the patient complained of headache. In the other, the temperature rose to 99.8° F., following an injection of neptal and to 100.2° F., following an injection of novurit, although the patient noticed nothing. The patient with cirrhosis of the liver with ascites complained of generalized abdominal discomfort and pain and a feeling of 'depression' for two days after the administration of each of the diuretics.

With regard to the novurit suppositories, two patients complained of slight local discomfort for a few minutes after insertion, though the suppositories were retained well. On four occasions there was a tendency to have one to three small evacuations of the bowels during the eight hours after the insertion of the suppository. The suppository, of course, was returned with the first evacuation, but not, as a rule, until it had been retained for two hours. Only two patients complained of more than slight discomfort. One patient, on his second admission, complained that he had 'terrible' pains after the suppositories on his previous admission, but he had made no complaint at the time and none of the nursing staff had heard of it. This was also true of the other patient who, after his fifth suppository, complained for the first time of local burning pains.

Failures. In only five patients was there no diuretic response. Of these, three were in extremis when admitted to hospital, one, a child, with heart

failure in acute rheumatism, one in advanced heart failure with arterio-sclerotic heart disease, and one in the terminal stages of carcinoma of the liver. The fourth had acute coronary thrombosis and developed incontinence, so that it was impossible to obtain an accurate estimation of the urinary output, although the state of the bed on the two days on which novurit was given showed that it was great. The remaining patient was a girl with rheumatic heart disease, who had only a slight degree of failure on admission, and no oedema at the time.

TABLE IX

Showing the Twenty-four Hours Urinary Excretion Following the Administration of Organic Mercurial Diuretics in Chronic Bronchitis Without Congestive Heart Failure

Case.	Novurit suppository.	Novurit.	Salyrgan.	Mersalyl.	Neptal.
	oz.	oz.	oz.	oz.	oz.
1	62				103
	72				
	90				
2	84	80	67	23	
3	51	80	60	68	
	66				
	60				
	66				
	47				
	37				
Average diuresis	63.5	80	63.5	45.5	103
In c.c.	1,800	2,270	1,800	1,290	2,930

Ammonium chloride was given with each diuretic.

Another method of assessing the unsatisfactory results is to compare the output following the mercurial preparations with the average output for the patient. On this basis 12 out of 208 novurit suppositories produced a twenty-four hours diuresis smaller than the 'average normal output' for the patient. This represents eleven patients. With a single exception a satisfactory diuresis was invariably obtained with the suppositories at some other time during their stay in hospital. With novurit, salyrgan, and neptal there were no instances in which the twenty-four hours urinary output was less than the 'average normal output', while with mersalyl there was one example—a patient with chronic bronchitis without heart failure.

Chronic bronchitis without congestive heart failure. The results in three such cases are shown in Table IX, from which it can be seen that in none was a striking diuresis obtained, the maximum being 103 oz. (2,930 c.c.) in a patient who also had a positive Wassermann reaction. There was no clinical evidence in this group of direct relief of dyspnoea or cough following upon the administration of the mercurial preparation, such as has been reported by Pellissier and his co-workers (87).

A theophyllin preparation. Although it is generally recognized that there is little comparison between the potency of the organic mercurial diuretics and the theophyllin preparations, one of these preparations was included.

The one chosen was deriphyllin, because it was available as a suppository. Deriphyllin is described by the manufacturers as 'concentrated water-soluble theophylline-oxyamine'. 1 c.c. = 0.412 gm. of deriphyllin, while the suppository contains 0.618 gm.

TABLE X

Showing the Twenty-four Hours Urinary Excretion Following the Administration of a Theophyllin Derivative (Deriphyllin)

Case.	Deriphyllin suppositories.			Intravenous deriphyllin (2 c.c.).		
	With ammonium chloride.	Without ammonium chloride.	Total.	With ammonium chloride.	Without ammonium chloride.	Total.
	oz.	oz.	oz.	oz.	oz.	oz.
1					24	24
2		44	44			
3	66		66	60		60
4		33	33		51	51
5					32	32
6		48	48			
7		140	140		124	124
8		36	36		28	28
9					16	16
Average diuresis	66	60.2	61.2	60	45.8	47.9
In c.c.	1,880	1,710	1,740	1,700	1,300	1,360

The results are summarized in Table X, from which it is seen that the average twenty-four hours diuresis for the six patients receiving the drug intravenously was 61 oz. (1,730 c.c.), while for the seven cases receiving the suppository the corresponding figure was 48 oz. (1,360 c.c.). Details of Case 7 will be found in the list of individual cases that follows this section. The patients in this group were selected because they all had a considerable degree of oedema and were representative of the various forms of heart failure included in the entire series.

Illustrative Cases

The following have been selected for detailed consideration because they present important features already mentioned.

H.G., Male, aged 25. Chart I.

Mitral stenosis. Auricular fibrillation. Failure. In-patient on three occasions during the preceding year on account of failure. Three weeks, swelling of abdomen. One week, increasing dyspnoea.

On admission. Afebrile, anasarca, ascites, liver enlarged. Pulse-rate, 90. Electrocardiogram: auricular fibrillation. Blood-pressure 140/90 approximately. Radioscopy: no hydrothorax. Urine, trace of albumin.

Progress. The patient was given various mercurial diuretics, but no digitalis, and the oedema completely disappeared, the liver being no longer palpable in eleven days (see Chart I).

F.J., Male, aged 27. Chart II A and B.

Mitral stenosis. Auricular fibrillation. Failure. Five months swelling

of right thigh and leg, palpitation and dyspnoea. Five weeks, recurrence of swelling, spreading to scrotum and abdominal wall.

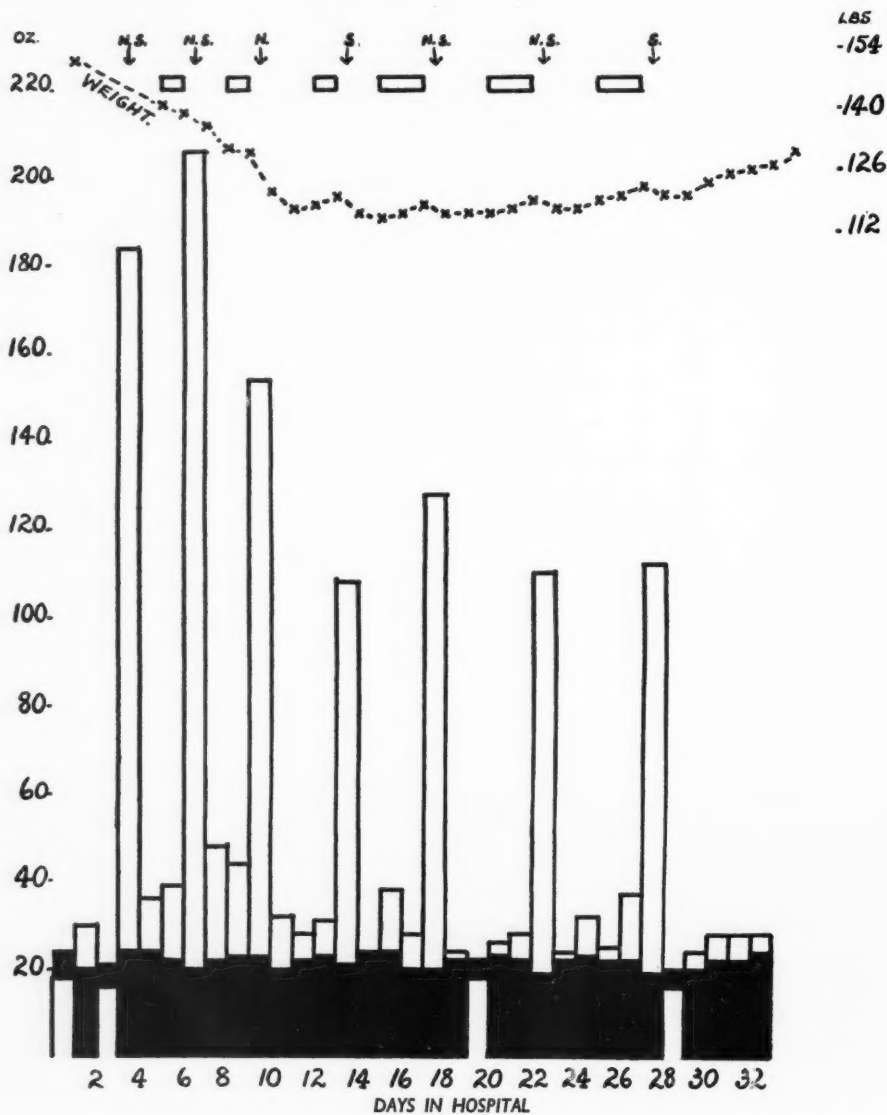


CHART I.

N.S. = Novurit suppository
 N. = Novurit
 S. = Salyrgan

Ammonium chloride
 Urinary output
 Fluid intake

On admission. Oedema of lower limbs, scrotum, and lumbar region, ascites, liver enlarged. Pulse-rate 64. Electrocardiogram; auricular fibrillation.

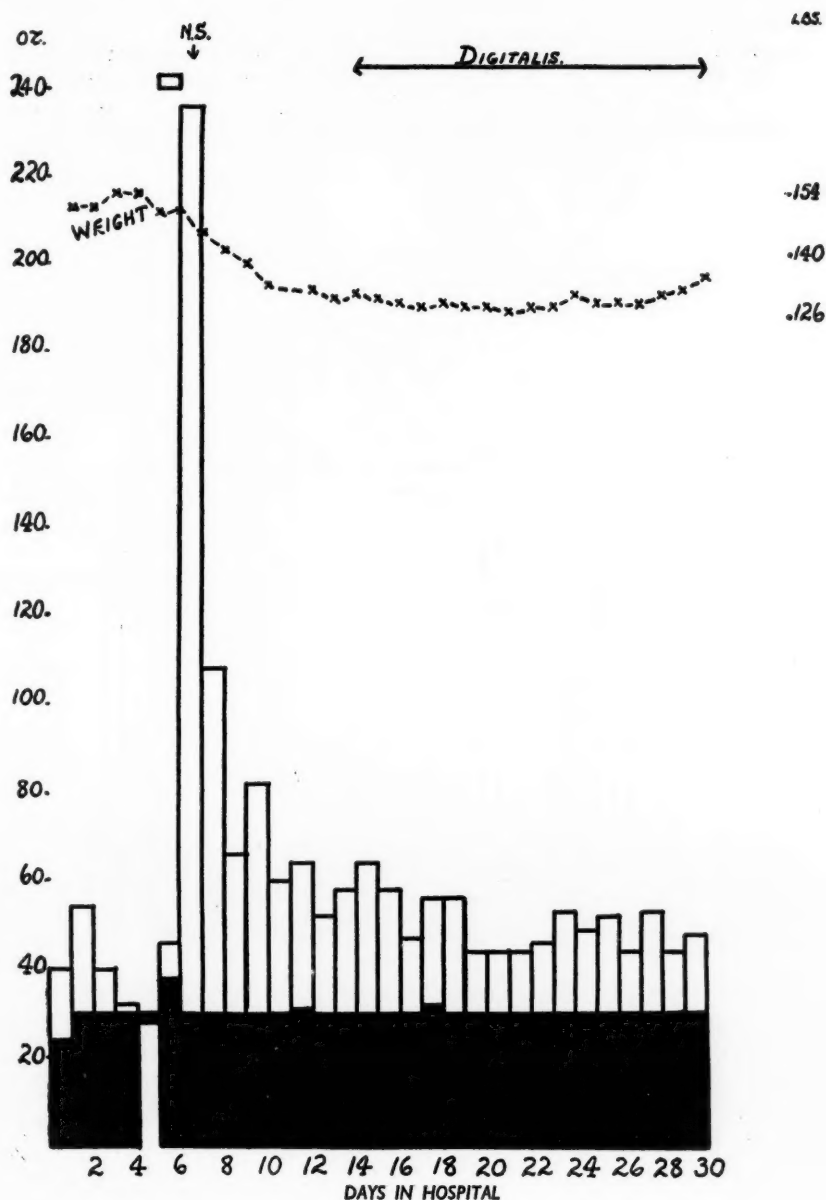


CHART II A

Radioscopy; no hydrothorax, right dome of diaphragm raised. Urine, haze of albumin.

Progress. Patient was given a novurit suppository, which was followed by a diuresis of 236 oz. (6,700 c.c.) during the subsequent twenty-four

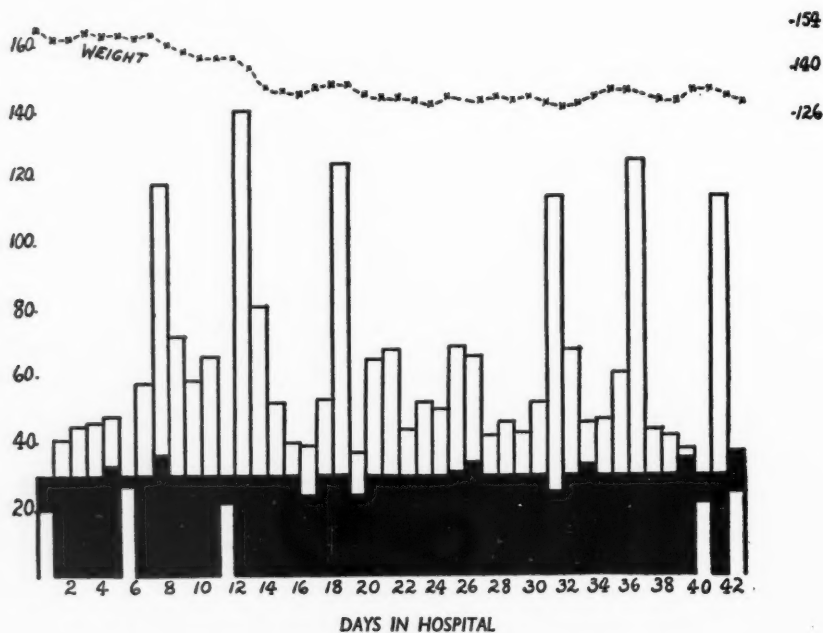


CHART II B.

N.S. = Novurit suppository
Nep. = Neptal
D.S. = Deriphyllin suppository
D. = Deriphyllin

Ammonium chloride
Urinary output
Fluid intake

hours. During the following seven days he lost 28 lb. (12.7 kg.) in weight. Two months after discharge, having taken digitalis regularly in the interval, he was re-admitted with a history of swelling of the feet and stomach, cough, and dyspnoea for one week.

On re-admission. Anasarca, ascites, liver enlarged. Pulse-rate 82. Radioscopy: no hydrothorax.

Progress. This time digitalis therapy was instituted immediately. During the first week, while the patient was having digitalis alone, there was a loss

OZ.

LOS.

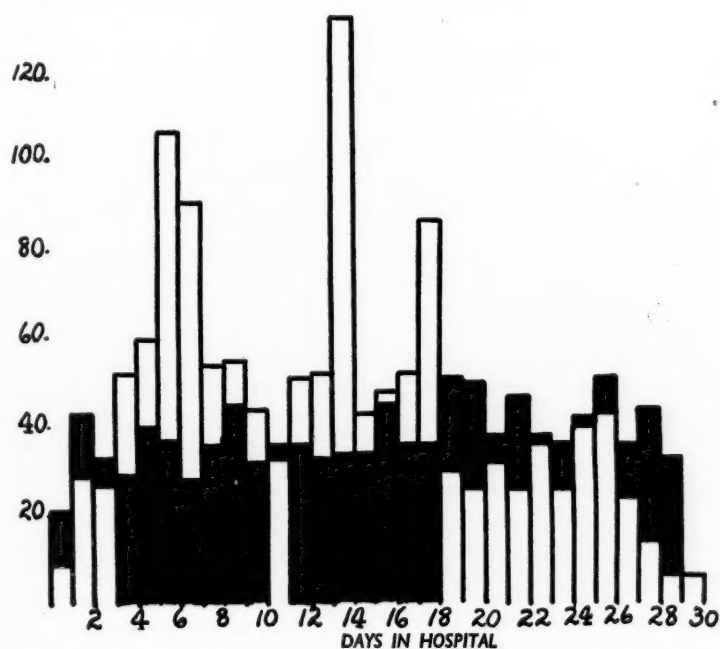
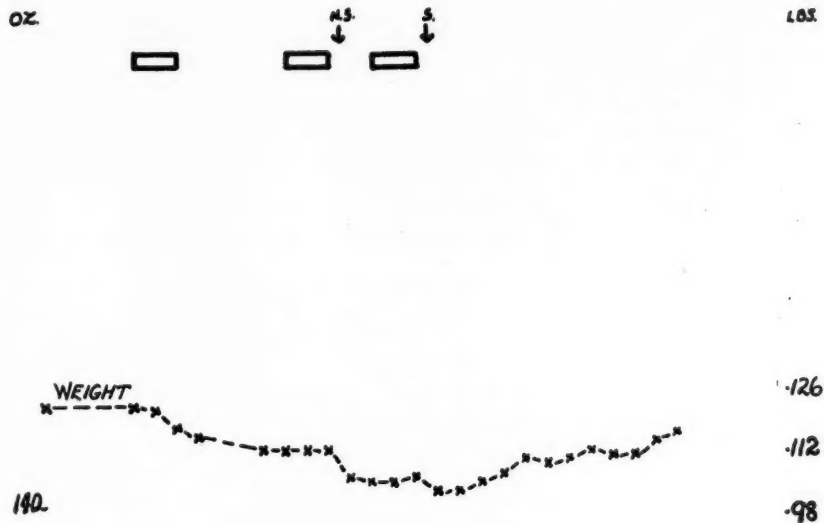


CHART III A

N.S. = Novurit suppository
S. = Salyrgan

Ammonium chloride
Urinary output
Fluid intake

of weight of 2 lb. (0.9 kg.), but no clinical evidence of diminishing oedema. Further therapy was then instituted, as shown on the chart, and within two weeks he had lost 19 lb. (8.6 kg.), the ascites had disappeared, the liver was much smaller, and there was only a trace of oedema in the legs.

The interesting features are:

1. The marked diuresis following a novurit suppository, the largest diuresis in the whole series.
2. The practically complete disappearance of oedema following upon one suppository on his first admission.
3. The more gradual diuresis on the second admission.
4. The comparatively large diuresis following deriphyllin and a deriphyllin suppository.
5. The absence of any diuretic response to normal saline (2 c.c.) intravenously. This measure was adopted to show whether the intravenous injection of an inert substance would provoke a diuresis.

A.H., Male, aged 64. Chart III A and B.

Aortic stenosis. Bundle-branch block. Normal rhythm. Failure. In-patient eighteen months before on account of failure. Six weeks, recurrence of dyspnoea. Two weeks, cough.

On admission. Oedema of legs and lumbar region. Liver enlarged. Pulse-rate, 80. Electrocardiogram: normal rhythm, right bundle-branch block (old terminology). Blood-pressure, 120/90. Radioscopy: no hydrothorax, hila prominent.

Progress. The administration of ammonium chloride for two days (gr. 120 (8 grm.) on the first day and gr. 90 (6 grm.) on the second) was followed by a diuresis of 112 oz. (3,180 c.c.) on the second day and 91 oz. (2,590 c.c.) on the third. Later, a novurit suppository, given after a similar dose of ammonium chloride, was followed by a diuresis of 133 oz. (3,780 c.c.). The maximal loss of weight during his stay in hospital was 19 lb. (8.6 kg.). Four months after discharge, he was re-admitted on account of recurrence of failure.

On re-admission. Orthopnoea, anasarca, liver enlarged. No hydrothorax.

Progress. On this occasion the patient was given no ammonium chloride and the maximal diuresis with the mercurial diuretics was 126 oz. (3,580 c.c.). The loss in weight was 23 lb. (10.4 kg.). The interest here lay in the definite diuresis with ammonium chloride on the first admission to hospital and the prolonged diuresis with mersalyl on the second admission. This is the patient referred to on p. 335, who, on his second admission, complained of discomfort with the novurit suppository given during his first stay in hospital.

S.D., Female, aged 49. Chart IV.

Mitral stenosis. Auricular fibrillation. Failure. In-patient three months before on account of failure. Since discharge, increasing swelling of legs and orthopnoea. Three weeks swelling of abdomen.

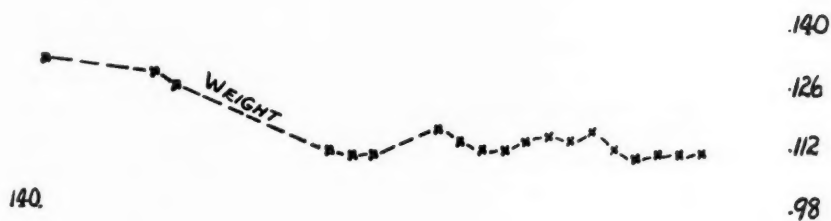
On admission. Orthopnoea, jaundice, oedema of legs and lumbar region, liver enlarged. Ventricular-rate, 160. Electrocardiogram, auricular fibrillation. Blood-pressure, 135/85, approximately. Bilateral hydrothorax.

Progress. On admission this patient was acutely ill. From the chart (IV), it will be seen that, in spite of full doses of digitalis and strophanthin, there was no diuresis until a novurit suppository was given, this being followed by a diuresis of 145 oz. (4,120 c.c.). In spite of a fatal termination on the twentieth day, this patient lost practically all her oedema and the liver was no longer palpable.

OZ.

M.
↓S.
↓N.
↓

LBS.



140.

.140

.126

.112

.98

120.

100.

80.

60.

40.

20.

2

4

6

8

10

12

14

16

18

20

22

24

26

28

30

DAYS IN HOSPITAL

CHART III B

M. = Mersalyl
 S. = Salyrgan
 N. = Novurit

□ Urinary output
 ■ Fluid intake

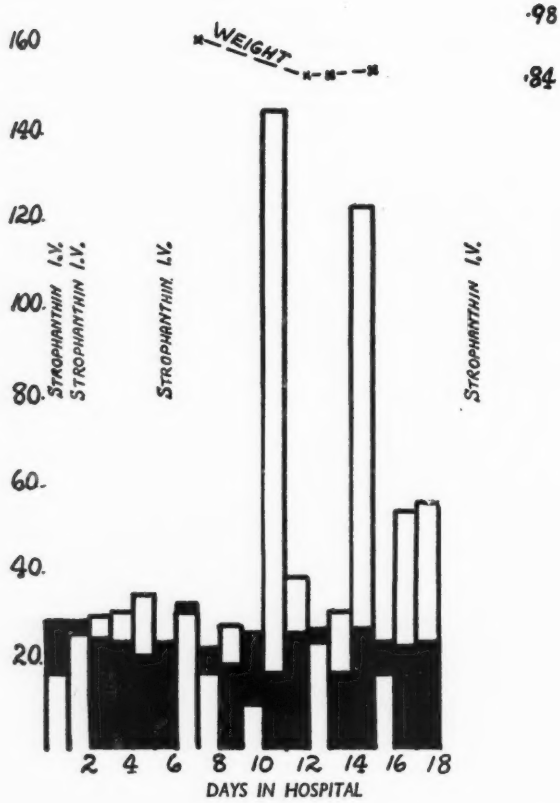
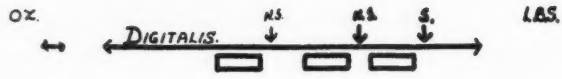


CHART IV

N.S. = Novurit suppository
S. = Salyrgan

Ammonium chloride
Urinary output
Fluid intake

Discussion

An attempt has been made to assess the value of the organic mercurial diuretics in cardiac dropsy, and there is no doubt that they provide a safe and potent measure for its relief.

Concerning the relative merits of the various members of this group, the results of this investigation show that, of the intravenous preparations, those which contain theophyllin tend to produce a rather larger diuresis than the non-theophyllin group. Thus the average twenty-four hours diuresis per injection was 105 oz. (3,000 c.c.) (53 injections) and 101 oz. (2,860 c.c.) (11 injections), for novurit and mersalyl respectively, and 94 oz. (2,670 c.c.) (71 injections of salyrgan and 9 injections of neptal) for salyrgan and neptal.

The results concerning novurit suppositories confirm and amplify the preliminary report on the subject issued from this department (85). That report was based upon the results in 10 patients with congestive heart failure, all of whom are included in this study and to whom forty-two suppositories were administered. The average twenty-four hours diuresis in these cases was 87.2 oz. (2,470 c.c.) for novurit suppositories, 121.1 oz. (3,435 c.c.) for novurit, and 91.8 oz. (2,600 c.c.) for salyrgan. These figures may be compared with the extended results shown in Tables V and VI, and already described on pp. 331-2. It is clear that the diuresis with the suppositories is not so great as with the same preparation given intravenously, in spite of the fact that the suppositories contain more than twice as much of the preparation than the 2 c.c., which is the usual amount given intravenously,—0.5 gm. compared with 0.2 gm. Absorption from the rectum, however, must be less than from the blood-stream, and in addition it will be remembered that the suppositories contain no theophyllin. This suggests that an enhanced diuresis might be obtained by giving theophyllin by mouth simultaneously with the administration of the suppository. It is interesting to note that the largest diuresis in the entire series—236 oz. (6,700 c.c.)—followed the use of a novurit suppository.

Mercurial suppositories should take a place in the treatment of cardiac oedema, the main advantage being their simplicity of administration, which obviates the disadvantages inherent in intravenous or even intramuscular therapy. These disadvantages include the risk of leakage into the subcutaneous tissues, the risk of sclerosis of the vein with repeated intravenous injections, the fact that in some cases oedema of the upper extremities prevents intravenous therapy, and the remote risk of nerve injury in intramuscular therapy. In general practice there are obvious advantages in rectal administration compared with intravenous injections, while an intelligent patient may be instructed to insert the suppository himself according to medical advice. Preparation for the suppositories is simple, either an aperient two nights before or an enema a few hours before; either method is equally effective. In an emergency they can be used without any preparation, though the resultant diuresis will not be so large.

The difficulty of obtaining adequate controls renders it difficult to judge the optimum dosage of ammonium chloride. Much larger numbers would be required, and even then there are so many varying factors concerned in the ultimate result that no definite result might be obtained. As has already been suggested, the individual response to ammonium chloride probably depends on the state of the acid-base equilibrium of the patient at the time at which the salt is given. The use of ammonium chloride does increase the diuresis following the use of the mercurial diuretics. There is no inherent advantage in continuous administration or in extreme doses. Equally satisfactory results are obtained with the use of 60-90 gr. (4-6 grm.) daily for two or three days preceding, and on the day of, the administration of the mercurial salt. Such moderate dosage obviates the risk of 'acidosis' and the risk of digestive disturbances. Of these latter there has been no experience in this series. If, for reasons of urgency or difficulty with the patient either from inability to swallow tablets or because of nausea, ammonium chloride cannot well be administered in preparation, there should be no hesitation in using the mercurial injection or suppository without its aid. Diuresis will be produced in the absence of ammonium chloride, although it is seldom so profuse, and a longer series of injections will be required.

The results of digitalis therapy in combination with the mercurial diuretics were unexpected. One assumed that in failure, at least with auricular fibrillation, the use of one of the digitalis group in addition to a mercurial diuretic would enhance the diuresis. Yet the average diuresis proved to be greater in the group which received no digitalis than in the group where it was given. The numbers may be small, but they are unselected. The only suggestion of selection for digitalis therapy was that there was a slight bias in favour of cases with auricular fibrillation, a bias which, on general principles, should favour the digitalis group. The general rule on this point was that the earlier patients in the series had no digitalis, in order to observe the effect of the mercurial diuretics alone, while the later cases received digitalis. Considerable importance should be attached to the results in the 19 patients who had periods both with and without digitalis, the average diuresis for the mercurial diuretics in the digitalis periods being 89 ounces (2,530 c.c.), compared with 86 ounces (2,440 c.c.) in the non-digitalis periods. In view of the importance of the subject, it would be unjustifiable to draw any more definite conclusion than that I have obtained no evidence that the administration of digitalis enhances the diuresis obtained with the organic mercurial diuretics in cases of congestive heart-failure.

It has been objected to the organic mercurial diuretics that, while they do produce a powerful diuresis, this only lasts for one day and that subsequently there is such a diminution in the urinary output as practically nullifies the first day's diuresis. Such a contention is baseless. As is evident from Table VIII, the diuresis on the second day after these diuretics is above,

while that on the third day is only slightly below, the 'average normal output' for the patient. On the other hand, it is evident that the diuresis only persists for one day (36).

Although cardiac oedema is the major indication for the use of the organic mercurial diuretics, it must not be forgotten that these preparations are also of value in the early stages of heart failure before oedema has become clinically apparent. They are serviceable in patients with dyspnoea of cardiac origin, nocturnal dyspnoea, or enlargement of the liver. No such patients without oedema were included in the present series, but in those patients with such symptoms and signs in addition to oedema, there was considerable relief of dyspnoea as well as disappearance of the oedema. Again, it was often noted that, although there was no clinical oedema, yet considerable diuresis and a noticeable fall in weight followed the administration of a mercurial diuretic.

The main lesson learned from this investigation is that the organic mercurial diuretics are entitled to a position in the forefront of our treatment of cardiac oedema and not merely a secondary position to digitalis or any other drug. They belong to the first line of attack and no longer yield precedence to digitalis. They are not mere adjuvants of digitalis and should no longer be classed with such measures as tapping of the chest and abdomen or mechanical drainage of the legs. Except where the heart itself is infected or in the terminal stages of heart failure, cardiac oedema will always respond to the organic mercurial diuretics and they constitute the first indication in treatment. Digitalis will nearly always be required for its inimitable effect upon the heart-muscle to combat the underlying failure which produced the oedema, and to help to prevent its recurrence, but, instead of one reliable remedy for cardiac oedema, we have now two, one acting on the general and renal circulation and the other directly on the kidneys.

Summary and Conclusions

1. The therapeutic value of the various organic mercurial diuretics, known by the trade names of salyrgan, neptal, novurit, mersalyl, and novurit suppositories has been investigated in 66 patients, 61 of whom had congestive heart failure with oedema. Of these, 33 had auricular fibrillation, and 28 had normal rhythm.

2. The average twenty-four hours excretion of urine per intravenous injection of 2 c.c. was for salyrgan 2,670 c.c. (94 oz.), for neptal 2,670 c.c. (94 oz.), for mersalyl 2,860 c.c. (101 oz.), and for novurit 3,000 c.c. (105 oz.).

3. The intramuscular route was seldom employed, but of 18 injections of neptal, nine were intramuscular and nine were intravenous. The average twenty-four hours diuresis per injection was 2,670 c.c. (94 oz.) for the intravenous group and 2,190 c.c. (77 oz.) for the intramuscular group.

4. Mercurial (novurit) suppositories were successfully employed on 208 occasions with an average diuresis per suppository of 2,360 c.c. (83 oz.).

5. Almost without exception the administration of ammonium chloride, 60-90 gr. (4-6 grm.) daily, for the two or three days preceding and on the day of the administration of the mercurial diuretic, resulted in an increased diuresis.

6. The administration of digitalis had no appreciable effect upon the diuretic response to the mercurial diuretics. Even when patients with auricular fibrillation were separately considered, the diuretic response was little affected by digitalis.

7. No serious toxic effects were observed during this investigation.

8. The organic mercurial diuretics are safe and efficient and have an almost universal application in the treatment of cardiac oedema. There is little to choose between the various preparations now available, except that those containing theophyllin are rather more active.

9. The dose, either intravenously or intramuscularly, is 2 c.c. of the solution as supplied by the manufacturers. The intravenous route is preferable. Two clear days should elapse between the injections (or the suppositories). Preliminary small doses are not required. If local conditions preclude the use of an undiluted injection, it is better to make use of the suppositories.

10. Mercurial (novurit) suppositories are satisfactory and easily administered, though the resulting diuresis is less than from an injection. They should, when possible, be preceded by an aperient two nights before or an enema a few hours before.

11. The optimum dosage of ammonium chloride is 20-30 gr. (1.3-2 grm.) thrice daily (i.e. gr. 60-90 (4-6 g.) daily), for two or three days preceding, and on the day of, the administration of the mercurial diuretic. For practical purposes this means continuous administration when the mercurial preparation is being given regularly on every third day (i.e. with two-day intervals).

12. Mercurial diuretics appear to act as efficiently in dispersing oedema whether digitalis is being given or not, although digitalis is generally indicated and should be given because of the failure. Indeed, the mercurial diuretics should take precedence even over digitalis where oedema is the prominent feature in congestive failure. Hydrothorax or ascites, as well as anasarca, will respond to these preparations, which should make the use of paracentesis, skin puncture, or Southey's tubes a rare necessity. Where there is cardiac asthma, orthopnoea, and enlargement of the liver—yet without external oedema—they should be used; and for incipient heart failure they find a place with digitalis in preventing the onset or recurrence of oedema.

The work upon which this paper is based was carried out during my tenure as Paterson Research Scholar and Chief Assistant in the Cardiac Department of the London Hospital, and I am deeply indebted to Dr. John Parkinson for his advice and help.

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STUDIES IN GRAVES' DISEASE

I

ALTERATIONS IN GASTRIC SECRETION AND
CORRELATED BLOOD CHANGES¹

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DISTURBANCES in the function of the thyroid gland have been shown to produce an effect on gastric secretion, and the relation of hyperthyroidism to a diminished gastric secretion and achlorhydria has attracted a certain amount of attention. In this investigation this relation has been studied further and an attempt has been made to correlate changes in the blood with the gastric findings.

Oliver and Wilkinson (1933) consider hyperthyroidism to be one of the most important endocrine causes of achlorhydria and hypochlorhydria. Moll and Scott (1927) investigated the test-meal findings in 50 cases of Graves' disease and found that 19 of the cases showed anacidity and 15 hypoacidity. The theories advanced by these authors to explain this diminished gastric secretion include overaction of the vagus, producing hastening of the stomach contents through the stomach and duodenal regurgitation, and the inhibitory effect of sympathetic stimulation. An association of decrease in acidity with a short duration of the disease was noted. Lerman and Means (1932) gave alcohol test meals to 50 cases of toxic goitre and estimated the acidity in the samples withdrawn at 10-minute intervals. They found anacidity in 38 per cent. of their cases. When correction was made for the age groups of the patients, the proportion showing anacidity rose to 45.6 per cent., compared with a figure of 12.6 per cent. in normal subjects. They found that anacidity was more common in the older patients and in those with the highest basal metabolic rates. They suggested a nervous origin for the disturbance and quoted Lewit's suggestion that the achlorhydria might be due to an anatomical alteration of the structure of the stomach by lymphocytic infiltration.

Allen and Wilkinson (1933) in similar investigations found that 36 per cent. of their cases were achlorhydric. They found a definite relation between the occurrence of achlorhydria and the duration of the symptoms. When their patients were re-examined three months after operation the proportion of achlorhydric cases had fallen to 10.5 per cent., showing that there was a prompt recovery of the acid function of the stomach. These

¹ Received April 3, 1937.

authors suggested over-stimulation of the sympathetic and damage to the gastric mucosa as possible causes of the failure in acid secretion. Berryhill and Williams (1932) found that of 35 patients with exophthalmic goitre, 69 per cent. had achlorhydria. Post-operative investigation showed return of acid into the stomach in ten days in 16 per cent. of the cases. In the remaining 53 per cent., the acid reappeared within two months of operation. They assumed that secretory function was resumed when thyroid hyperfunction ceased, as judged by decrease of pulse-rate and metabolic rate. There was no correlation between the presence of achlorhydria and total iodine dosage, duration of illness, or rate of metabolism. They suggested that the condition was a secondary effect of autonomic imbalance, but admitted that there might be a direct toxic effect on the stomach.

Experimental work on animals subjected to thyroid feeding has given similar results. Thomsen (1925) showed in dogs a progressive diminution of the volume of secretion but could prove no change in the pH of the gastric juice. Truesdell (1926) found that feeding thyroid extract to dogs led to a decreased gastric secretion. Hardt (1916) showed a decrease in acidity and rate of secretion. Moll and Flint (1928) produced achlorhydria by thyroid administration. Chang and Sloan (1927) were able to demonstrate a decrease in the amount of secretion and percentage of hydrochloric acid by similar experiments.

A uniform alteration in the gastric secretion in myxoedema has not been so generally observed. Brown (1930) reported achlorhydria to be present in three out of five cases, Lockwood (1925) in six cases out of 10, and Stone (1928) in four out of 16 cases. Lerman and Means (1932) showed 75 per cent. of 17 cases of myxoedema to have achlorhydria compared with 15 per cent. of normal individuals of the same age groups. They found no relation to age but associated the degree of anaemia present with the anacidity. Allen and Wilkinson (1933), on the other hand, in their investigations of five cases of myxoedema, found an excessive secretion of acid to be present. Katz (1920) also found myxoedema to be associated with hyperacidity and was able to get a return to normal secretion by administration of thyroid extract. Levy (1929), investigating 10 cases of myxoedema with B.M.R. values ranging between - 13 per cent. and - 25 per cent. found hyperacidity in nine of them. Animal experiments have also supported the association of hypersecretion with hypothyroidism (Chang and Sloan 1927).

Cowgill (1934) found that when hyperthyroidism was produced in dogs, there was an increase in the vitamin B1 requirements. Lecoq and Joly (1936) have shown that a lowering of the respiratory quotient and an increase of the basal metabolic rate can be produced by diets deficient in vitamin B1. The symptoms of a vitamin B1 deficiency include those associated with gastro-intestinal atony and decrease of gastric secretion, and the possibility must be considered that the high incidence of gastric achlorhydria and hypochlorhydria in thyrotoxicosis may be due to a vitamin B1 deficiency.

Experimental

In this investigation the basal metabolic rate (B. M. R.) has been studied in relation to the test-meal findings and the values of blood and plasma chlorides before and after operation. Cases of primary thyrotoxicosis were taken as far as possible; those of toxic adenoma and secondary thyrotoxicosis being rejected. The ages of the patients ranged from 14 years to 62 years, and the duration of symptoms varied from a few months to 15 years. Only one male subject was investigated. One case of myxoedema was examined. Control investigations were made on a varied group of cases.

When the incidence of hypoacidity in thyrotoxicosis was confirmed it was decided to estimate the effect of administration of massive doses of vitamin B1 on the gastric secretion. A preparation of vitamin B1 known to be active in curing monkeys on vitamin B1 deficient diets, was given intramuscularly to two severe cases of thyrotoxicosis before operation.

Methods

The B. M. R. was estimated by the Douglas-bag method. Blood was then taken without stasis from the median vein under paraffin for estimation of plasma chloride and bicarbonate reserve, and a specimen for the whole blood chloride estimation was taken in the usual way. The blood chlorides were estimated by the method of Van Slyke (1923) and the bicarbonate reserve by that of Van Slyke and Neill (1924). After the blood samples had been taken, a Ryle's tube was passed into the stomach and the fasting juice was withdrawn. Histamine acid phosphate was then injected: the original dose was worked out at 0.1 mg. per 10 kg. of body-weight, but later a standard dose of 0.3 mg. was found to be adequate and to give rise to no troublesome symptoms. Continuous aspiration was employed as described by Bloomfield and Polland (1933) and the specimens were collected over 10-minute periods. In our cases as in those of Bloomfield and Polland (1933) regurgitation of base into the stomach did not occur and the acid and total chloride concentrations gave parallel figures. The investigations were repeated nine to eleven days after the operation.

Results

Twenty-six cases were examined. The results are given in Chart I. The B. M. R. values ranged between +6.2 per cent. and +74 per cent. before operation. Fifteen cases had basal metabolic rate determinations before and after operation. All these cases except Case I showed a fall in the rate after operation. In 11 cases there was a rise in the R.Q. level post-operatively, two showed no change and in two cases there was a fall in the R.Q.

CHART I

No.	Age.	Duration.	B.M.R.	R.Q.	Bicarbonate reserve.	Test meal				Blood	
						Free acid.		Total acid.		Total chloride.	Whole blood chloride mg. per 100 c.c. NaCl.
						Max. % N/10 acid in c.c.	Total vol. in c.c.	Max. % N/10 acid in c.c.	Total vol. in c.c.		
GRAVES' DISEASE											
Pre-operative and post-operative results											
1 F	30	3 years	+16*	0.665	63	10	1.5	40	8.7	94	609
2 F	35	5 years	+21	0.695	69	62	19.7	80	28.1	118	580
			+65	0.765	—	0	0	4.8	0.81	62	442
3 F	29	4 months	+49	0.665	64.2	9.4	0.86	14.2	2.93	92	491
4 F	26	1 year	+48	0.740	72.9	60	17.6	84	26.9	121	545
			+15	0.605	1	94	51.2	112	59.9	141	562
5 F	35	5 years	+47.5	0.675	—	0	0	12	2.74	143	—
			+31.5	0.650	—	38	25.4	62	37.9	196	—
6 M	25	5 months	+60	0.720	73.9	0	0	7.2	1.1	87	—
			+22.8	0.640	—	82	48.3	100	65.3	136	437
7 F	49	1 year	+69	0.700	—	76	72.3	94	93.4	118	520
				—	—	0	0	3	1.64	72	568
8 F	29	5 years	+6.2	0.670	—	6	0.25	24.5	2.0	110	—
			+19.0	0.672	—	23	7.9	50.8	20.5	111	—
9 F	14½	1 year	+38	0.775	73	50	28.7	70	43.1	123	—
			+6	0.880	74	26	5.36	46	15.8	84	581
10 F	39	6 years	+70	0.752	—	48	26.17	60	44.6	98	550
			+12	0.695	—	0	0	34	10.0	62	592
12 F	22	3 months	+23	—	—	18	7.6	36	17.7	90	568
				—	—	—	—	—	—	—	570
13 F	46	2 years	+19	—	—	—	—	—	—	—	454
				—	—	—	—	—	—	—	450
14 F	48	2 years	+49	—	—	—	—	—	—	—	552
				—	—	—	—	—	—	—	511
				—	—	—	—	—	—	—	600
				—	—	—	—	—	—	—	561
				—	—	—	—	—	—	—	620
				—	—	—	—	—	—	—	505
				—	—	—	—	—	—	—	436

* Upper figures pre-operative, lower figures post-operative.

[illegible]

CASE OF MYXOEDEMA

11 F	Before treatment	— 35.5	0.680	—	44	20.8	66	43.2	138	82.8	406	522
Age 58												
	After thyroid $\frac{1}{2}$ gr. 8 times daily	+ 2.5	0.678	—	42	5.8	76	19.0	130	38.0	482	580
	After thyroid 1 gr. 6 times daily	+ 12.0	0.690	—	36	6.2	44	8.7	—	—	511	602
	After thyroid $\frac{1}{2}$ gr. 6 times daily for 8 weeks	— 0.8	0.710	—	34	7.4	57	20.31	118	54.5	450	552

The bicarbonate reserve was estimated in four cases. In all of these the pre-operative figure obtained was low. There was a rise in the value after operation.

Plasma chlorides. The values obtained, expressed as NaCl., ranged between 0.543 and 0.620 per cent. with an average figure of 0.576 per cent. The normally accepted figures for plasma chloride are from 0.560 to 0.620 per cent., so that the majority of our cases showed values on the low side of normal. After operation the plasma chloride values fell in 18 out of 21 cases. The average fall was 34 mg., the post-operative range being from 0.488 to 0.580 per cent. In the remaining three cases two showed a rise. The figures obtained for plasma chlorides are of greater significance than those of the whole blood because they represent a real alteration of chloride balance. The whole blood chloride is dependent in part on the degree of anaemia present, and this latter factor was not taken into account in these investigations.

Whole blood chlorides. The values obtained pre-operatively were between 0.421 and 0.511 per cent. with an average of 0.459 per cent. The average normal range is given at between 0.450 and 0.530 per cent. so that the whole blood chlorides also gave results on the low side of normal in our cases. In 15 out of 20 cases this value fell still farther after operation, the average drop being 26 mg. Four cases showed a rise in value, but since no blood counts were taken it is not possible to explain the alteration; in the remaining case there was no change. The alterations in the plasma and whole blood chlorides are shown in Chart I.

Test meals. Eighteen cases were given test meals pre-operatively: eight of the cases showed complete achlorhydria after histamine injection: seven cases showed hypoacidity. The values for free acid in the hypoacid cases ranged from 10 to 32 per cent. Three cases showed an excess of acid. These three cases were of short duration, the time since onset being in two cases three and in the other case five months. The figures obtained for total acidity showed parallel results, 11 out of 18 cases hypoacidity, four normal acidity, and three hyperacidity. The total chloride output was also low. One of the most striking features of these meals was the small total volume of gastric juice secreted.

The estimations were repeated eight to ten days after partial thyroidectomy. In 12 out of the 15 cases with achlorhydria or hypochlorhydria there was a return or increase in free acid in the samples taken. A rise of acid occurred also in one of the three cases of short duration which had shown hyperacidity before operation. One achlorhydria showed no change, the achlorhydria remaining: the patient had developed a septic throat after operation which probably accounted for the persistent achlorhydria. One case of hypochlorhydria also did not change. One meal was discarded owing to failure to obtain standard conditions. The post-operative figures for total acid and total chloride showed similar increases. The results are given in Chart I. The increase in the volume of free acid secreted after

thyroidectomy was important. A total secretion of 143.36 c.c. of free acid in 16 cases pre-operatively rose to a volume of 383.57 c.c. after operation.

Myxoedema

One case only was investigated. The results of the test meals and blood chlorides are given in Chart I. The response to thyroid therapy in this case was accompanied by changes in gastric acidity and blood chlorides opposite in direction to those obtained in the hyperthyroid cases treated by thyroidectomy. With thyroid feeding the volume of gastric juice diminished and the acid values fell. The blood chlorides showed a progressive rise. The higher the dose of thyroid the more pronounced were the changes. Three months after discharge from hospital when she had been on a dose not quite sufficient for her needs, the acid values and volume had risen and the whole blood and plasma chlorides fallen again.

Cases Treated with Parenteral Vitamin B₁

Two cases (Nos. 39 and 40) were given before operation, daily intramuscular injections of vitamin B₁, total dosage 4,000 and 2,500 international units respectively. In neither case was there any increase in the output of acid from the stomach. It is possible that these doses were inadequate.

Case Histories

No. 4. Female, aged 26. History of swelling of the neck for one year accompanied by diarrhoea, excessive sweating, loss of weight, and palpitations. On admission to hospital the patient was restless, exophthalmos was marked and there was tachycardia. The thyroid was moderately enlarged to form a symmetrical swelling of firm consistency with pulsation of the vessels.

Investigations. The B.M.R. was +48 per cent. Test meal showed complete achlorhydria after histamine injection. Electrocardiogram revealed a short rest time but no gross changes. Partial thyroidectomy was performed. The histological report stated that there was widespread severe hypertrophy and hyperplasia of the epithelium of Graves' type. There was an uninterrupted recovery. The post-operative B.M.R. was -47.5 per cent. In the post-operative test meal there was a maximum free acidity of 38 per cent. in the gastric juice and the volume excreted was increased.

No. 10. Female, aged 39. History of swelling of the neck appearing suddenly after a severe shock nine months previously: she had complained of palpitations, breathlessness, sweating, and tremor since. On examination there was exophthalmos, tremor, tachycardia, and a symmetrical bilateral swelling of the thyroid.

Investigations. The B.M.R. was +70 per cent., the R.Q. being 0.700. The test meal showed complete achlorhydria after histamine injection: the percentages and volumes of total acid and total chlorides were low. The plasma chlorides were 0.592 per cent. and whole blood chlorides were 0.470

per cent. The electrocardiogram showed a severe thyrotoxic condition of the heart. A partial thyroidectomy was performed with quadruple ligation of the arteries. The pathologist's report on the gland stated that widespread hyperplasia and hypertrophy of the epithelium of Graves' type were present. Colloid storage was much diminished; few lymphorrhages were present. Progress after operation was uneventful. The B.M.R. fell to +12 per cent. Post-operative test meal showed a maximum of 18 per cent. free acid and increases in the volumes and percentages of total acid and total chlorides. The plasma chlorides fell to 0.568 per cent. The whole blood chlorides remained at the same level.

No. 40. Female, aged 31. Treated with vitamin B1. History of swelling in the neck for three months. She had also noticed protrusion of the eyes, palpitations, sweating, tremor of the hands, and nervousness. Recently she had suffered from diarrhoea. There had been considerable loss of weight. On examination she had a moderate firm enlargement of the thyroid gland. Exophthalmos was marked, the skin was moist, a fine tremor of the hands was present. The heart was over-acting, the pulse-rate being 130. The electrocardiogram showed no gross changes. She was given 2,500 units of vitamin B1 intramuscularly in the five days prior to operation with no increase in gastric acidity. Partial thyroidectomy was performed. Histological examination of the gland revealed severe epithelial hyperplasia and hypertrophy of Graves' type. A few lymphorrhages were present. The progress of the patient after operation was satisfactory.

No. 11. Female, aged 58. Myxoedema. For two years she had noticed swelling of the face. She had felt cold even in a warm room. Her hair had become thin and dry and the skin dry. Her appetite was good but she suffered from constipation. Her weight had increased: she was breathless on exertion. On admission the temperature was 97 and the pulse-rate was 58. Her appearance was typical. The cheeks and nose were reddened, the face looked swollen, and the lips were thick. Her hair was very thin, dry, and brittle, and the skin was dry and scaly. Her voice was deep and the speech was slow. The heart was not enlarged and the sounds were normal. An electrocardiogram showed a low voltage record with no preponderance. The urinary output was reduced to about 13 ounces daily.

She was put on to thyroid siccum $\frac{1}{4}$ gr. six times daily, rising to $\frac{1}{2}$ gr. eight times daily, then 1 gr. six times a day, which was later reduced to 1 gr. three times a day. Her facies changed completely. The bloated look and stupid expression disappeared, speech became more rapid, and the voice less deep. On 6 gr. of thyroid daily, a mild degree of thyroid intoxication was produced. There was a loss of 1 st. 2 lb. in five weeks on thyroid therapy. The output of urine was almost doubled.

The results of the test meals and blood chlorides are set out in Chart I, and show changes in the reverse direction to those observed in Graves' disease.

Control experiments were carried out on a varied group of cases and Chart II shows the results obtained.

The first eight cases, excepting Case 24, all gave normal blood chloride figures which could not be correlated with the gastric acidity or the volume of gastric juice secreted. The administration of 15 grm. of sodium chloride three times daily to a case with normal blood chlorides (Case 22) led to no significant change in their values. Case 31 showed the effects of feeding in

CHART II
Controls.

Case No.	Nature of illness.	B.M.R.	Test meal				Blood	
			Free acid.		Total acid.		Whole blood chloride mg. per 100 c.c. NaCl.	Plasma chloride
			Max. % N/10 acid in c.c.	Total vol. secreted in c.c.	Max. % N/10 acid in c.c.	Total vol. secreted in c.c.		
20	Severe anaemia after rectal haemorrhage	—	88	22.0	100	27.3	472	577
21	Healthy student	-11	92	55.7	110	104	442	582
22	After 14 days on exhepa	-11	78	75.1	92	111	460	598
22	Case of starvation	-2.4	0	0	37	11	487	609
	After 20 days treatment with 15 gm. of sodium chloride daily	+22	0	0	16	7.9	495	614
24	Pyloric stenosis with vomiting	—	84	—	94	—	403	479
25	Post-operative result	—	70	—	—	—	495	—
26	Nasal polyp	—	84	155	102	190	455	548
28	Duodenal ulcer	—	84	24	82	36	499	595
	Anxiety neurosis	-3	60	24	82	36	490	575
29	After Lugol's iodine for 15 days	-18	64	10	82	19	490	574
	Rheumatoid arthritis	-17	21	10	45	22	467	607
31	After Lugol's iodine for 14 days	-2.4	18	7	58	22	463	600
	Severe anorexia nervosa	+42	7	—	17	—	398	508
32	After treatment by diet	-16	—	—	—	—	464	560
	Disseminated sclerosis	—	—	—	—	—	424	531
	After pyrexia due to pyrifur	—	—	—	—	—	450	554

starvation on the blood chlorides. Cases 32 and 24 were of interest as they showed changes in the blood chlorides due, in the former case, to concentration by excessive sweating with adequate chloride intake and in the latter to a loss of chloride from the body resulting from severe and prolonged vomiting. In the latter case, when the vomiting was controlled by operation the blood chloride value rose rapidly to normal.

Discussion

The results of the investigations of 18 cases of thyrotoxicosis showed that 44.4 per cent. had an achlorhydria and that 38.8 per cent. had a diminished acid secretion in the stomach. The diminished acid secretion was associated with a small volume of juice. The bicarbonate reserve in the few cases in which it was estimated was low. The values for the chlorides of blood and plasma were in the low ranges of the normal. The basal metabolic rates were high and the respiratory quotients were low. After operation there was a fall in the basal metabolic rate associated with a rise in the respiratory quotient. There was a return of acid secretion in the achlorhydric cases and an increase of acid in the hypochlorhydric cases. The volumes of free acid, total acid, and total chlorides secreted by the stomach showed a well marked increase. The blood and plasma chloride levels fell still further after operation.

In the interpretation of these results certain experimental work must be considered. Apperley (1936) has demonstrated that the gastric acidity is largely governed by the carbon-dioxide content of the blood. An alkalosis, either compensated or uncompensated, can be produced by a primary oxygen deficit due to overbreathing, fever, early stages of oxygen deficiency, and certain cardiac diseases. Such an alkalosis is associated with a rise of pH of the blood, a decrease of the bicarbonate reserve, and a lowered gastric acidity. Experiments on animals, Browne and Vineberg (1931), Mosonyi, Gunther, and Petranyi (1935) showed that a lowering of the carbon dioxide of the blood, produced in their cases by hyper-ventilation, led to a reduction in the acid values in the gastric secretion and a lowering of the blood chlorides, while inhalation of carbon dioxide, on the other hand, produced hyperacidity in the stomach and a rise of blood chlorides. In the investigations recorded in this work on thyrotoxic patients there was a definite correlation between an increased basal metabolic rate, a lowered bicarbonate reserve, a decreased gastric acidity, and lowered blood chlorides. This correlation can be explained on the basis of the work of Apperley and others quoted above, since conditions of increased pulmonary ventilation, oxygen want, and in some cases, cardiac deficiency as well, were present in the thyrotoxic patients examined. Attempts, however, to correlate in any one case, the rise of gastric acidity with the drop in blood chlorides have not succeeded in these cases. A similar lack of correlation between acid values in the gastric secretion and those of the blood chlorides was found by

Jacobsson and Ostachowa (1936), who investigated the changes in cases of anacidity, normal acidity, and hyperacidity.

Although the alterations in bicarbonate reserve and the gastric acidity may be accounted for by change in the carbon-dioxide content of the blood, other factors must be considered, especially since the behaviour of the blood chlorides cannot be explained by this means. The effect of sympathetic stimulation and the influence of other ductless glands must be borne in mind. Stimulation of the sympathetic nervous system causes inhibition of the movements of the gastro-intestinal tract and decrease of gastric secretion. Brown (1930) states that the symptoms of hyperthyroidism may be interpreted in terms of an increased sympathetic drive due to action of an altered thyroid hormone. This causes an over-sensitization of the thoracolumbar sympathetic, which over-rides the normal antagonistic action of the parasympathetic and gives rise to stimulation of the inhibitory acid secretory fibres of the stomach. The secretion of the adrenal gland is undoubtedly concerned in the activation of this sympathetic response. Experiments by Squier and Grabfield (1932) have shown that thyroid feeding to dogs causes an increase of both the cortex and the medulla of the adrenal gland. Crile (1928) considers that hyperthyroidism is a fundamental disorder of the adrenal gland and would call the disease thyro-adrenal disease. Marine (1931) states that normally the cortex of the adrenal acts as inhibitor to the thyroid. If this were so, the condition of hyperthyroidism would imply the existence of cortical deficiency. The condition of the adrenal in Graves' disease has not been closely investigated. At post-mortem examination, the gland has been noted to be smaller than normal and the reduction is seen in both cortex and medulla. It is possible that in the early stages of hyperthyroidism there is a hypertrophy of both cortex and medulla, that the cortex of the gland becomes exhausted first and that certain symptoms of deficiency arise together with the characteristic symptoms of established thyrotoxicosis. Certainly many of the symptoms of thyrotoxicosis may be explained as being on the one hand symptoms of medullary stimulation, and on the other hand, e.g. the pigmentation and asthenia, as symptoms of cortical deficiency. A cortical failure would explain the relatively low values obtained for plasma and whole blood chlorides in our cases. Harrop (1936) has shown recently that the adrenal cortex is concerned with the movements of tissue and blood fluids. In cortical deficiency there is a drainage of plasma water into the extra cellular tissue outside the vascular system. With injection of cortical hormone the fluid shift is back into the plasma. This shift back of fluid into the plasma may be a factor in the fall of the plasma chlorides after thyroidectomy. In most cases the cortex recovers its function after thyroidectomy, although in rare cases the disturbance may proceed to Addison's disease. It is hoped to publish shortly the notes of a case of Addison's disease arising late in the course of Graves' disease.

The part played by the pituitary gland in the control of thyroid function

must also be considered. The thyrotropic hormone of the anterior pituitary, when injected into animals, produces a hyperplastic condition of the thyroid gland resembling Graves' disease. Exophthalmos occurs, the colloid of the gland is reduced, and there is a reduction of the iodine content. The anterior lobe of the pituitary also produces a hormone which influences the structure of the adrenal cortex. Collip (1935) has shown that an extract of anterior pituitary, capable of producing hyperplasia of the thyroid, produces also hyperplasia of the adrenal cortex. Crooke and Russell (1935) in their investigations on the pituitary gland in Addison's disease, found that in seven cases out of nine in which the thyroid gland was examined, there was evidence of excessive activity of the gland strongly resembling Graves' disease. The most important change in the pituitary gland found in the cases of Addison's disease was extreme reduction of the basophil cells. The pituitary gland probably also is related to the functional activity of the gastro-intestinal tract. Injections of posterior pituitary extracts have given rise in animals to haemorrhagic lesions of the stomach limited to the acid-bearing area (Dodds, Noble, and Smith (1934)).

The frequent association of gastric ulceration in cases of basophilic adenoma of the anterior pituitary has also been noted (Swan and Stephenson (1935)). There is evidence therefore that pituitary disturbances may be associated as well as thyroid disturbances with alterations of the gastric secretion. A close inter-relationship exists between pituitary, thyroid, and adrenal. In Graves' disease this balance is disturbed and the disturbance may have been initiated in any one of the principal glands involved. From the clinical side this view is substantiated by the fact that it is often possible to differentiate in cases of Graves' disease between those in which pituitary influences chiefly are at work, those in which the adrenal effect predominates, and those in which the thyroid gland itself is principally at fault.

Summary

1. Certain cases of thyrotoxicosis are associated with achlorhydria or hypochlorhydria. The total volume of gastric juice secreted is markedly reduced. Cases of short duration do not show these changes.
2. There is a recovery of the function of the stomach within ten days of thyroidectomy with increase in the percentage and volume of acid in the stomach. Septic complications may delay the return of acid.
3. The values of plasma and whole blood chlorides are in the lower ranges of the normal in thyrotoxicosis and there is a further fall after operation.
4. A rise of the pH of the blood due to hyper-ventilation, oxygen want, and cardiac disease would account for the fall in the gastric acidity and the low blood chlorides. Sympathetic stimulation also plays a part by inhibition of the gastro-intestinal tract. Adrenal cortical insufficiency may also be a factor in the causation of the low chloride values. A re-adjustment

of body fluids is suggested as a possible explanation of the post-operative fall of the blood chlorides.

5. Administration of massive doses of vitamin B1 was without effect on the acid secretion of the stomach in untreated cases.

We wish to thank Mr. Cecil Joll, Dr. Hare, and Dr. Jenner Hoskin for permission to investigate their cases in the wards and the cardiac clinic of the Royal Free Hospital. We are indebted to Roche Products Limited for supplies of vitamin B1.

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THE PSYCHOLOGICAL FACTORS IN ASTHMA-PRURIGO¹

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ONE of the most interesting trends in modern medicine has been the growing recognition of the importance of psychological factors in disease.

This statement applies very closely to the problem of asthma, in which such factors have been recognized for a long period. In 1698 John Floyer published the first edition of his book *A Treatise of the Asthma*; one of his principal chapter headings concerns: 'The evident Causes of the Asthmatic Fit, as the Air, Diet, Exercise, Passion, &c.' Describing the effects of passion he writes: 'The Passion of Anger makes the Spirits restless and apt to produce the Fit and the Asthmatics observe in themselves great restlessness of Spirits the day preceding the Fit. Fear, Sollicitude, and much Study discomposes the Spirits and produces a restlessness in them which may occasion a Fit.'

These are very shrewd observations, of far greater value than the statements of many later writers who mention, among a list of other causes of asthma, a psychological or nervous factor. Frequently, having thus paid lip-service to the importance of the mind, they proceed to disregard it completely both in theory and in practice. Another viewpoint which is frequently adopted is that asthma may be either physical or psychological (then usually termed hysterical). The possibility of the two factors being constantly intermingled does not seem always to be realized.

It has been said that asthma is not a disease but a symptom and its causes are therefore many. It is frequently found in association with other allergic manifestations such as hay fever and prurigo, and this is the type most commonly seen in children. The form of prurigo which occurs in these cases was first described by Besnier (1892). According to him the fundamental symptom was an intense itching, paroxysmal in character, intermittent with a regular seasonal variation, being worse in some cases in summer, in others in winter. The localization was characteristic in that the joint flexures, particularly the antecubital and popliteal spaces, were the sites chiefly affected, the skin in these situations becoming lichenified and often fissured. Besnier realized the close relationship of the condition to asthma and hay fever, and this view has been fully confirmed by modern writers (e.g. Barber (1929)). The whole group of symptoms as it is found, particularly in children, has come to be regarded as the 'asthma-eczema-prurigo

¹ Received April 14, 1937.

syndrome', and it is with asthma and prurigo of this type that the present work is chiefly concerned.

Research upon this subject was first undertaken in the Department of Psychological Medicine at Guy's Hospital about four years ago and it has been carried on steadily since that time. This paper is a report on some work carried out during a period of one year from September 1935 to September 1936.

The initial survey consisted of a group of twelve children suffering from asthma or eczema-prurigo or both together. It was found that in many of these cases nervousness was a leading complaint given by the parents about the children. Many of the children were 'only children' or were, for some other reason, in a position in the family in which they were much over-protected. When they were away from home they were often completely free from asthmatic attacks, but when they returned they relapsed at once. That this was due to the psychological, rather than to the physical, quality of their environment can be clearly shown by numerous examples. For instance, one child relapsed immediately when his parents came to take him away from a convalescent home where he had been free from symptoms. When the environment was studied psychologically and simple modifications made, the improvement was very striking. It was accordingly decided to investigate a larger group of such cases, and the assistance of a social worker and a psychologist was obtained through a grant from the Asthma Research Council. Twenty-five cases were studied and the results fully confirmed the earlier work. The parents were often markedly over-protective and over-anxious. Attention to these problems was followed by an improvement in the condition of the children. The patients themselves were nervous, over-anxious, and insecure, and their personality in this respect showed a curious similarity. They were also of more than average intelligence; the average intelligence quotient of the group was 108, being nearly twenty points above that for all the children who attended the clinic during the year. So impressive was the personality-likeness of many of the cases, that one began to speak very tentatively of an asthma-prurigo personality in which a high intelligence and an underlying aggressiveness was combined with over-anxiety and insecurity. Thus, from the psychological point of view, there appeared to be in the asthma-prurigo syndrome a certain type of personality and a certain type of environmental difficulty. Moreover, one found that by dealing as far as possible with the abnormalities which were found, it was possible to alleviate the symptoms.

The object of the first part of the present work was to study the 'asthma-prurigo personality' in more detail. It seemed important to know, first, whether on close analysis any special personality features could really be found which were common to many of the cases. Secondly, what was the significance of such personality features, if any. Were they, for example, merely secondary to the over-protection and other environmental difficulties found in the cases? Or could they be considered to be to some extent

primary features of the individual's endowment? If this were true, they might be one part of the asthma-prurigo 'constitution' which has so often been postulated. And lastly, what relationship had these findings to the actual asthma attacks.

The latter question was the scope of the second part of the paper in which a study was made of the actual setting, physical and psychological, in which asthma attacks occurred. Thus it was hoped to assess the relative importance of the findings which had been made and to present a dynamic picture of the psychogenic factors in the condition. The possibilities of psychological treatment should follow logically from this.

A Study of the Asthma-prurigo Personality

Methods. Neither intelligence nor personality can properly be measured in a single test. The definition of personality given by the *Oxford English Dictionary* is 'the distinctive individual character'. It is necessary, therefore, to study a number of tests and to seek in them the basic characteristics of the individual. Unfortunately in a standard test situation the distinctive personality qualities of an individual tend to be subdued. It is therefore necessary to depend upon the reaction of the individual to his daily life and difficulties both as observed by himself and by others. Such reactions are what Adolf Meyer has called 'experiments of nature', and their use implies a careful biographic study of the individual's life and circumstances both past and present. The more objective this can be, the greater its value.

On the whole, this biographic approach is probably the best method for the study of personality available at the present time. Here it has been used as fully as possible. The behaviour of the individual has been recorded particularly in relation to concrete situations. The observations of others, concerning the patient, have also been noted. These have included the observations of relatives and friends as a part of the biographic study and also special observations made in the clinic. Of these the routine intelligence tests were of great value. Here the patients were presented with a standard situation in which their behaviour could be observed and compared with that of others. In some cases it was also possible to observe the children at play, thus obtaining much further material.

The method of history taking was invariably the same. At the first interview the complaint was recorded in the actual words of the patient and relatives. No leading questions were asked at this stage and the parent was encouraged to tell everything that seemed wrong with the child. The result was that first of all a statement about asthma or skin trouble was obtained and then frequently complaints of another kind. In a high proportion of the cases these were statements about nervousness. When the parent had come to the end of the complaint, the detailed history was

TABLE I

Composition of Group and Results of Treatment

Case.	Sex. Age.	Period of study.	Number of visits.	Reason for referral.	Severity.	Duration of condition.	Result of treatment.	Improve- ment.	Case.
1	M 5	1 year	15	Asthma	Frequent moderate	1½ years	Occasional moderate	++	21
2	M 8	1 year	8	Asthma	Occasional severe	Infancy	Free from symptoms	++	22
				Prurigo	Constant moderate	Infancy	Constant moderate	0	
3	M 5	5 months	5	Asthma	Periodic moderate	Infancy	Free from symptoms	++	23
				Prurigo	Periodic moderate	6 months	Occasional mild	++	24
4	M 5	4 months	3	Asthma	Periodic severe	2 years	Occasional severe	+	
				Prurigo	Occasional mild	Infancy	Occasional mild	0	25
5	M 15	9 months	6	Asthma	Frequent severe	13 years	Periodic severe	+	26
6	M 10	11 months	2	Asthma	Frequent severe	5 years	?	?	27
7	M 6	9 months	26	Asthma	Frequent severe	5 years	Occasional severe	++	28
8	M 6	8 months	5	Prurigo	Constant severe	4 years	Free from symptoms	++++	29
9	F 12	11 months	6	Prurigo	Constant moderate	Infancy	Free from symptoms	+++	30
10	M 9	7 months	3	Prurigo	Constant severe	Infancy	Occasional mild	+++	
11	M 8	3 months	2	Asthma	Frequent severe	7 years	?	?	
12	M 13	10 months	6	Asthma	Frequent severe	Infancy	Occasional mild	+++	
13	M 7	5 months	4	Asthma	Periodic moderate	4 years	Periodic moderate	0	
14	F 12	5 months	1	Asthma	Occasional severe	5 years	?	?	
15	F 13	6 months	3	Asthma	Periodic severe	Infancy	Periodic severe	0	
16	F 6	7 months	4	Asthma	Occasional severe	4½ years	Free from symptoms (6 months)	++	
17	M 12	10 months	11	Asthma	Occasional severe	7½ years	Free from symptoms (10 months)	++	
18	M 13	9 months	3	Asthma	Occasional moderate	Infancy	Free from symptoms (6 months)	++	
				Prurigo	Constant moderate	Infancy	Free from symptoms	+++	
19	M 8	11 months	12	Asthma	Occasional mild	1 year	Free from symptoms (10 months)	++	
				Prurigo	Constant severe	Infancy	Constant severe	0	
20	M 5	4 months	2	Asthma	Occasional moderate	Infancy	Free from symptoms (4 months)	+	
				Prurigo	Constant moderate	Infancy	Occasional mild	+++	

TABLE I (continued)

Case.	Sex. Age.	Period of study.	Number of visits.	Reason for referral.	Severity.	Duration of condition.	Result of treatment.	Improve- ment.
21	F 9	1 year	11	Asthma	Periodic severe	Infancy	Periodic severe	0
				Prurigo	Constant severe	Infancy	Constant mild	++
22	M 3	1 year	4	Asthma	Occasional moderate	1 year	Free from symptoms	++
				Prurigo	Constant severe	Infancy	Occasional mild	++++
23	M 10	1 year	4	Prurigo	Constant severe	Infancy	Constant severe	0
24	M 8	1 year	6	Asthma	Occasional moderate	Infancy	Free from symptoms	++
				Prurigo	Constant moderate	Infancy	Free from symptoms	++++
25	M 4	1 year	3	Prurigo	Constant mild	Infancy	Free from symptoms	+++
26	M 10	6 months	9	Asthma	Periodic moderate	7 years	Occasional moderate	+
27	M 3	11 months	3	Prurigo	Constant mild	Infancy	Occasional mild	++
28	F 5	4 months	9	Prurigo	Constant moderate	4 years	Periodic moderate	+
29	M 4	6 months	17	Prurigo	Constant severe	Infancy	Constant mild	++
30	F 5	9 months	17	Asthma	Periodic severe	3 years	Occasional severe	++

continued in the ordinary way. Special attention was directed to obtaining from the parent descriptions of concrete situations in which the child had played a part. Such situations graphically described afford, as was stated above, the best possible 'personality study'. At the end of the history more specific questions were asked concerning the child's personality, but leading questions were again carefully avoided.

In day to day discussions with the parents the same method was used. Here many concrete illustrations of the child's personality in action could be obtained whilst they were fresh in the parent's mind. These were considered to be of great value since they depend but little upon a subjective evaluation by the examiner. In this way it was possible to obtain an idea of the personality of the child at home. In the clinic, the value of the observations made during the routine psychological tests has been mentioned. Every child who comes to the clinic, no matter what the nature of his problem, is given an intelligence test. For children over five years of age the Terman modification of the Binet Scale, together with a group of performance tests, is used. For those under five years the Merrill Palmer Scale is generally employed. Each child is tested individually, and careful notes are made concerning his behaviour during the test. The psychologists have experience of large numbers of children of every type. They are usually not aware of the nature of the problem presented by the child. Their observations concerning his personality have therefore the highest

objective value. The actual results of the intelligence tests were also of great importance in these cases, and will be considered at the end of the personality study.

A series of observations were also made upon some of the children in a playroom. The results of this experiment can also more conveniently be summarized at a later stage.

Results. As has already been stated, a group of 30 children was used for the study. The size and composition of the group were both chance determined, no attempt having been made to regulate either the number or source of the cases. They represent all the children suffering from asthma-prurigo who were seen by the writer during a period of one year. There has been no deliberate selection of material. The cases came from the usual variety of sources, some were referred directly to the Department of Psychological Medicine, some came from the Children's Medical Department, the Asthma and Skin Clinics. The group thus contains a representative selection of hospital patients.

In the first part of Table I is shown the sex, age, type, severity, and duration of the condition as well as the number of visits paid to the clinic. There are 23 boys and only 7 girls. A higher incidence in the male has been recorded by many writers both for asthma and for Besnier's prurigo. The age distribution is fairly even between the extremes of 3 and 15 years. The severity of the condition is graded as follows. Asthma is described as 'frequent' when attacks occur fortnightly or more often. 'Periodic' means that the attacks occur once in every two to four weeks, and 'occasional' less than one in four weeks. 'Severe' means that the child is totally incapacitated by the attack. 'Moderate' that he is partly incapacitated, e.g. from going to school, but does not have to remain in bed for the duration of the attack. 'Mild' that he is not much incapacitated and is able to go to school. Prurigo is graded as constant, periodic, or occasional, the latter representing very infrequent outbreaks. It is also graded as 'severe' when several skin areas are the seat of severe irritation, 'moderate' when one skin area is severely affected or when several are mildly affected, and 'mild' when one area is slightly affected.

The duration of the condition is expressed in terms of years except when it dates vaguely into early childhood in which case the term 'infancy' is used. The total number of attendances recorded by each case during the year is noted in the third column. The total for all the cases is 210. The mass of material which has to be presented is therefore very great. For the sake of clarity it has been tabulated as far as possible. Nevertheless it must be emphasized that each case is to be considered as a whole. The records were made as separate biographic studies without reference to special groups of characteristics, the latter are employed solely for convenience of presentation.

In Table II the results of this personality study are set forth. The sign in the second column indicates whether or not nervousness was a spon-

taneous leading statement made by the parent about the child. Columns 3 to 6 include the personality traits which emerged from various parts of the study. Column 3 includes the complaint and the material obtained at the first interview. Column 4 includes the material obtained from subsequent day to day interviews. Column 5 contains the observations made during the psychological test. Column 6 contains those made during individual play. As far as possible, the exact adjective used originally is employed in the table. It was, however, not possible to record here in full the statements made, since their repetitiveness and diffuseness would make the table very bulky. It is therefore proposed to group under a number of headings in the text the outstanding personality traits and then to add more detailed samples of the descriptions given.

First of all there is the general term 'nervousness'. This is mentioned as a leading complaint by 23 out of 30 patients. This fact is interesting, for it confirms quite strikingly the impression recorded by so many authors that children with asthma-prurigo are 'nervous'. When the succeeding columns in the table are studied some much more specific observations emerge.

1. *Statements concerning the motor activity of the children.* Under this heading have been grouped together descriptive terms such as 'restless', 'very active', 'gets excited' (definitely meaning excessive movement), 'tense', 'highly strung' (meaning here a liability to sudden outbursts of movement). Statements of this type occur in respect of 22 of the children, appearing nineteen times in Column 3 and eight times in Column 4. In most cases the activity consisted of multiple small movements such as are covered by the terms 'tense', 'highly strung'. Many of the children described by parents in such terms appeared, when first seen, to be quiet and subdued. It was only later, on watching them closely, that an underlying restlessness could be observed. In some cases too, as treatment progressed, the subdued or covertly restless child became boisterous and over-active. This change was frequently associated with clinical improvement. It may be noted that restlessness was not particularly observed by the psychologists. It seemed that when the children were interested in, and actively engaged upon, a task their restlessness disappeared. As soon as they were unoccupied they became again restless, irritable, and often started to scratch themselves.

Examples of descriptive statements given are as follows:—

Case 8. 'Very quiet but jumpy if he is by himself, goes nearly mad when he is with other children.'

Case 22. 'A picture of restless, untiring energy. Always jumping and twitching, even in his sleep.'

2. *Statements concerning 'anxiety', &c.* Twenty-one children were described as being 'over-anxious', 'unself-confident', 'afraid', 'insecure'. In the complaint such statements are made concerning 16 cases. In 11 cases anxiety is not mentioned as a prominent characteristic, and in three positive statements of boldness occur. In later records 10 children are clearly shown

TABLE II
Personality Study of the Group

Case.	Nervous- ness.	Personality as observed in				I. Q. Binet Perf. Test.	Environmental factors.
		Complaint.	Later records.	Psychological tests.	Play.		
1	—	Excitable aggressive fearless headstrong disobedient	Night terrors jealous dominating aggressive restless	—	<i>First</i> Quiet <i>Later</i> Bold aggressive	119 90	Only son. Constant family quarrels over his management
2	+	Restless lively solitary	Over-anxious worried demanding dominating	Insecure	—	125 114	Much over-protected by mother
3	+	Restless fearful crochety solitary	(Becoming gradu- ally) bold venturesome bumptious over-active	—	—	72 92	Only child. Over-pro- tected by mother
4	+	Highly strung very active bad tempered aggressive eager solitary dominating	—	Very dominating uneasy fear of failure	—	125 107	Only child. Over-pro- tected
5	+	Afraid easily worried	Anxious unself-confident keen to succeed	Unself-confident afraid to commit himself	—	97 106	Only child. A brother died in infancy. Mother very anxious
6	+	Afraid of school	—	—	—	—	No obvious factors

7	+	Timid excitable afraid solitary	Afraid of dark anxi- ous about school <i>Later</i> Becoming very ag- gressive restless	Won't commit him- self in case he is wrong	<i>First</i> Very timid <i>Later</i> cautious play <i>Later</i> Bold aggressive	108 100	Only son. Not over- protected but very jealous of baby sister. Quite well away from home
8	+	Afraid whining jealous solitary	Gets very excited in presence of other children, nearly goes mad	Dominating weeps to attract mother into room	—	115 140	Only son. Some over- anxiety about him
9	—	Irritable sensitive dominating	<i>Later</i> Over-active and cheerful	Quiet settled down well	—	111 130	No obvious factors
10	—	Very active bold sociable	—	—	—	104 93	No obvious factors
11	+	Restless active solitary anxious dominating	—	Lacks self-confidence worried over failure	—	113 130	Very nervous, over- anxious mother
12	—	Excitable solitary	—	Anxious fear of com- mitting himself	—	110 166	No obvious factors
13	+	Highly strung afraid	—	Perfectionistic dislikes admitting failure	—	117 107	Mother constantly worrying over his health. Much re- stricted
14	+	Restless over anxious keen to succeed	—	—	—	100	Only child. Over-pro- tected
15	+	Irritable over-anxious afraid solitary	Worried over school work very over- anxious	Afraid to commit her- self, evades difficulty	—	92 97	Some maternal over- anxiety
16	+	Anxious afraid solitary	Worries over school work	Afraid to commit her- self	—	110 126	Over-anxious, over- protective mother

TABLE II (continued)

Case.	Nervous- ness.	Personality as observed in				I. Q. Binet Perf. Test.	Environmental factors.
		Complaint.	Later records.	Psychological tests.	Play.		
17	—	Timid over-anxious solitary	Worries over school work afraid of fail- ing	Tense insecure anxious careful dislikes failure	Quiet careful anxious unself-confident	112 132	Only child. Over-pro- tected by very anxious mother
18	—	Restless fidgety 'a terror', sociable	<i>Later</i> Vigorous interest in active sports very active	Worried and anxious	—	83 95	No obvious factors
19	+	Highly strung irritable solitary	Very dominating needs to be centre of picture, uses symptoms for this purpose	Worried insecure anxious	Aggressive very dominating	102 100	Only son. Over-pro- tected by anxious parents
20	+	Lively active over-anxious afraid solitary	—	Friendly co-operative	—	132 110	Only child. Over-pro- tected by anxious parents
21	+	Irritable jealous friendly	Worried over lessons unself-confident tries to dominate her friends	Afraid of doing any- thing wrong	—	107 89	Over-anxious mother
22	—	Restless astonishing energy jumping and twitching	Dominating family demanding atten- tion	Avoids difficulties	—	100 M. P.	Only child. Nervous, over-anxious mother
23	+	Restless irritable sleepless solitary	Dominating de- manding attention jealous	—	—	114 114	Jealous of younger brother

24	+	Anxious irritable solitary	Quarrelsome	Worried over-anxious fear of failure	—	119 150	Only son
25	+	Excitable restless solitary	Over-anxious aggressive dominating	—	—	95 M.P.	Only child. Sensible mother but much restricted by necessity
26	+	Shaky jumpy over-anxious solitary	Hot-tempered dominating demanding attention restless	Over-anxious hostile	—	102 102	Only son. Over-protected
27	—	Very energetic sociable	—	Obstinate demanding attention	—	104 M.P.	No obvious factors
28	—	Stubborn active solitary	Dominating demanding attention	Dislikes failure intensely	Demanding attention and admiration	116 107	Only child. Over-protected and a source of contention between parents
29	+	Very active restless dominating	Disobedient dominating attention over-active	Great dislike of failure	<i>First</i> Quiet and subdued <i>Later</i> Tremendous aggressive over-activity dominating and bullying	108 M.P.	Only child. Sensible mother. Somewhat over-anxious
30	+	Dominating over-anxious solitary	<i>First</i> Refuses to leave mother over-anxious <i>Later</i> Aggressive and talkative	Wary defensive	<i>First</i> Refuses to play <i>Later</i> Aggressive destructive play	115	Sensible mother. No obvious factors

to be over-anxious, and in the psychological tests 10 children also are described in similar terms. The expression 'insecure' which appears several times in this column appeared to indicate a general uneasiness and lack of self-confidence. It is remarkable how frequently the over-anxiety of the children occurred in relation to their school work. This is the more striking because, as will be shown, nearly all of them were of superior intelligence.

For example:

Case 2. 'So worried about the possibility of getting things wrong that he hardly does anything.'

Case 17. 'Worried because he can't do his homework properly. Worries because he does not do as well as some of the others.'

Case 21. The school teacher sent a report about this child which read as follows: 'She has nothing to worry about, she must remember that worry helps no one—be brave instead, grow a little more pluck and the worry will go.'

Closely allied to this characteristic was the attitude of the children towards success in the psychological tests. Very many of them showed so great a dislike of failure that they preferred to say nothing rather than to risk being wrong. They appeared to set themselves a very high standard from which they could not fall without personal discomfort. They would avoid the issue and turn the conversation at the critical point rather than risk making a mistake. Notes of this type of behaviour occur in 11 of the records.

3. *Irritable, aggressive, dominating behaviour.* The statement of irritability occurs frequently. It is a difficult term to define, but on analysis it proved, almost invariably, to signify behaviour of an aggressive type, a partial outburst of temper or an anger at being thwarted. Such aggressive dominating behaviour is recorded in 19 of the cases. It would appear at first sight to be completely unrelated to the anxiety just described. But this was not the case. Often the over-anxiety was part of a desire to excel over other children at school, i.e. a desire to dominate. The over-anxiety appeared when this desire was thwarted. Similarly many of the children showed an intense need to dominate their families and to be the centre of the picture. They would whine and cling to their mothers, appearing thoroughly over-anxious and insecure. But at such times it was demonstrated again and again that the underlying motive was a demand for attention rather than a fear of being left alone.

Examples:

Case 1. 'There is a free fight if they correct him at school. He is very jealous of his sister, mauls her about, threatened to kill her. Does everything he can to attract attention. Soiled himself deliberately.'

Case 28. 'Scratches herself to attract attention.' On one occasion, when mother is deliberately trying to disregard this, she says, 'Look, Mother, I've dug myself'.

Lastly it is interesting to note that 17 of the children were described as

being solitary in their play. This cannot be accepted by itself as an indication of any special personality trait since it must depend so greatly upon environmental factors which have yet to be analysed. Nevertheless, it may be said at once that the figure is a very high one.

Observations upon the Personality Features Revealed in Play

In a limited number of cases it was possible to make some observations upon the child's play. Before discussing the records obtained in this way, it will be necessary to explain the technique used. A room in the clinic is set aside for a certain part of the week as a play room. It is equipped with such elementary play material as sand, water, plasticine, dolls, doll's house, drawing and painting materials, toy soldiers, toy trucks, &c. The floor is covered with a canvas mat, and breakable articles of furniture are reduced to a minimum. The child is invited to come into the room by himself, and is told at the outset that he can do exactly what he likes except wilfully break windows or lights. The method has been adopted partly as a means of study of children's play and partly as a therapeutic weapon. Into this latter aspect it is not opportune to go at the present time, but it may be stated that the object of a 'play technique' is to enable the child to give expression to his fears and difficulties through play. With an adult it is possible to discuss such difficulties directly through speech, but with a child this is possible only to a limited extent. It is necessary to approach a child through the medium in which he is most at home, namely his play. No attempt is made to observe the child unseen by him. On the contrary the psychiatrist enters into active participation and discussion of whatever the child is doing. Each play session lasts about 50 minutes, and rough notes are made at the time which are subsequently amplified.

It might justly be claimed that other and better methods of experimental observation could be devised, but it is necessary to remember that the method had also to be used for purposes of treatment. The conditions of the experiment, such as it was, were constant in each case, and there was ample opportunity for comparing the results with those obtained in non-asthmatic children.

Several personality features emerged from this method of study. Nearly all of the children showed an initial over-anxiety and lack of self-confidence far greater than is usually seen. One or two of them would scarcely play at all, and others played very cautiously with a few toys in a corner of the room. At first there was very little aggressive play, and soldiers and cannon were treated carefully and often with alarm. After a while the children became more confident, and then their behaviour showed an aggressiveness and over-activity in marked contrast to earlier play. During this phase of vigorous activity, there was in most cases a striking clinical improvement. It was noted, however, that if their freedom of self-expression was curtailed or thwarted in any way there was often a return of symptoms even during the play session. For example, Case 29, when first seen in the company of

his mother, was very subdued, and clung anxiously to her. At the same time he appeared restless and tense and was constantly scratching himself. When allowed into the playroom he rapidly became over-active, noisy, and aggressive. At the same time, he ceased to scratch himself. When, however, he was thwarted by anything his symptoms quickly returned. One day, for instance, he was given a physical examination instead of being allowed to play at once. He cried, was sullen and tense, wriggled restlessly, and scratched himself vigorously.

It was the object of this 'play therapy' to enable the children to overcome their fears and anxieties, and to learn to control their aggressive impulses, so that ultimately they could meet difficult situations without symptoms. This will be discussed under the heading of treatment; meanwhile a summary of the personality features observed in play is included in Table II.

Discussion of Observations

It is now possible to summarize all this material. From a study of the records of these 30 children, it appears that certain personality characteristics are outstanding among them. Twenty-two children are described as over-active, restless, excitable. Twenty-one children are described as over-anxious, unself-confident, afraid, insecure, &c. Nineteen children are described as irritable, aggressive, dominating, &c. It was noted that as treatment progressed those who were originally described as tense, restless, irritable, became at times very active and aggressive. If thwarted by temporary or continued restriction the earlier pattern reappeared. It was also noted that the over-anxiety and aggressive dominating behaviour were often closely allied.

Such consistent personality findings point very strongly towards certain common psychological factors in these cases. They are not to be found in any unselected group of children. It is interesting, for example, to compare them with a group of similar observations upon non-asthmatic children. The first 30 non-asthmatic children seen in the Department of Psychological Medicine during the year 1936 furnish a convenient sample. There is no special selection in such a group, and there are no family groups which might bias the picture. If one studies the 'complaint' in these cases, recorded in exactly the same way, one finds that six of the children are described as restless, excitable, fidgety, or over-active; six as over-anxious or afraid, and four as bad tempered or aggressive. The corresponding figures from the 'complaint' in the asthma group are 19, 16, and 9. This comparison is not intended to be more than a concrete illustration of a clinical observation. It becomes even more striking when one realizes that the control group, if one may call it this, consisted of children specifically referred for psychological difficulties, whilst the original group was referred for asthma-prurigo.

In order to complete the picture of the personality of these 30 children, the numerical results of their intelligence tests must be added. In previous

work it was found that the average intelligence quotient of asthmatic children was considerably above the average for non-asthmatic patients. These further cases should supply important additional evidence of this result. The older children were tested both upon the Binet scale and also upon a group of performance tests. Small children were tested upon the Merrill Palmer scales. The results of these tests will be found in a separate column in Table II. The average intelligence quotient of the 25 children who were tested upon the Binet scale is 108.8. This compares with the figure of 108 for the previous group of cases. Thus there is strong additional evidence that the cases of asthma-prurigo seen in the Department of Psychological Medicine over a period of two years are of superior intelligence. The causes for sending these cases for examination have already been mentioned, and it is difficult to see in what way they differ greatly from the sources from which the bulk of the children seen in the Department are drawn. But the average intelligence quotient of these children is much lower, being for example, 89.0 for a total of 321 children seen during 1936. Therefore it seems valid to assume that patients with asthma-prurigo tend to be of intelligence above the average.

How far are these characteristics the product of environmental factors such as have been described in previous work? In some cases it has seemed that maternal anxiety and over-protection have been quite sufficient to account for the nervousness and characteristic behaviour of the child. Is it right, therefore, to regard the child as a potentially normal individual without inherent tendencies to behave in any special way? Strong support could be obtained from psychological and philosophical writers both for and against such a view. Indeed too much speculation about the origin of personality is apt to be very fruitless. The behaviour of an individual has been developed and modified by the constant pressure of his environment acting from the moment of his conception. We cannot entirely separate the tangled threads. We can only study the patterns they form at the moment of observation and from them try to deduce what has gone to their shaping. It has been shown in previous work that environmental difficulties play a special part in the asthma-prurigo syndrome and are closely related to the symptoms. It has also been shown that these difficulties tend to be of a particular type, that is, they are produced by an over-anxious, over-protective attitude on the part of the parents. The cases which have been studied in this paper are similar in this respect. Many of them show the same typical situational factors. In Table II a brief summary of the environmental difficulties found in the group is given. It will be seen that no less than 18 of the children come from families in which one or both parents are over-anxious and over-protective towards them. In a number of cases there are special reasons why this should be so, for example 10 of the children are 'only children' and are thus particularly precious, whilst similarly six others are 'only sons'.

Is this the explanation of the whole personality-type observed? At first

sight it might appear to be so, for there is no doubt about the relationship of the environmental factors to the symptoms. For example, Case 2 was quite free from attacks when away from his parents, whereas at home he constantly suffered. On the other hand when he went away from home *with* his parents he was just as bad as ever. Very many instances of this kind have already been quoted, and many more could be found in the present material. If the environmental factors are so closely bound up with the attacks, are they also responsible for the personality of the children or is this the result of a special endowment? In attempting to answer these questions one must first ask in addition whether it is reasonable to search for any special constitutional endowment in the asthma-prurigo patient. At this point one may profitably draw an analogy with the physical production of asthma. There are certain substances which are capable of producing an asthmatic attack if they are injected into sensitive individuals. These substances do not produce attacks in every one, but only in certain people.

It has therefore been postulated by many (e.g. Hurst) that there is a constitutional predisposition which renders an individual liable to asthma-prurigo; in other words, there is a special type of individual who develops the attacks. Attempts have been made on the somatic side to study the characteristics of this special type. Such attempts have not been very fruitful; most of the physical characteristics of the asthmatic are clearly secondary to the disease. But the concept of a special predisposition seems to offer the most reasonable approach to the asthma problem, and the fact that no definite somatic type has been isolated does not rob the idea of its value. In seeking the characteristics of a special individual type one need not devote oneself exclusively to physical measurements. It is as reasonable to undertake such a search from the psychological as from the physical standpoint. The search for special psychological features in a group of individuals becomes inevitably a search for a special personality type.

Here, in these cases, special personality features have been shown to exist. Can we then assume that we have isolated the personality features which are part of the asthma-prurigo constitution? This assumption cannot be made without further proof. For although a personality type has been found, it has not yet been shown to bear any relation to the constitutional endowment of the individual. As already stated, it might be secondary to the environmental factors and to the disease itself, just as a barrel-shaped chest is secondary to the disease. This is a frequent physical finding, but it cannot be used to demonstrate a constitutional type. Additional evidence must therefore be produced to show that the personality type is not merely a secondary feature of the condition.

In searching for such evidence, one fact is the high intelligence of the children. Here is an objective carefully standardized observation of something which, as far as one can see, is not modified greatly by the attitude of the parents or by the disease. The fact that it is, on an average, so much above the normal, suggests strongly that one is dealing with a special type

of individual. This discrepancy is very wide, since there is a difference of about 20 points between the average for 25 of these children tested on the Binet scale and that for 329 other children similarly tested, who attended the clinic during 1936. It does not seem possible to account for this discrepancy by any theories of special selection, age group, sex, or other factors. The intelligence of the five remaining children who were tested upon the Merrill Palmer scale is equally high. This high intelligence has been consistently found in all the groups of cases which have been studied, and it is a fact which would be difficult to explain save along the lines of a special constitutional endowment.

Another interesting observation is that one or two of the children who showed most typically the personality-traits which have been described were not the products of a difficult environment. For example, Case 30 was the child of a normal, rather stolid, and quite unanxious mother. She was an intelligent woman, and described clearly how the child had always clung on to her and demanded her attention in marked contrast to the child's elder sister, who was normal. There did not appear to be any clear environmental reason for this over-anxious demanding behaviour on the part of the patient. Similarly Case 29 'screams for attention' and has said to his mother, 'If I promise not to scratch, will you kiss me?' He was tremendously restless, over-active, and demanding in his behaviour, and his mother, a sensible woman quite able to cope with the behaviour of an ordinary child, was disturbed and sometimes overwhelmed by him. Case 15, a girl of 13, differed markedly from the other two children in the family in that she was always wanting to be with her mother and demanding her attention. The mother was somewhat over-anxious in her attitude towards her, but no more so than in the case of the other children. She herself commented upon this behaviour on the part of the child.

Examples of this sort make one feel that the personality-traits described do not depend entirely upon the environmental factors. It appears that the personalities of the children are such as to precipitate difficulty in their management, their attitude is often such that the parents would be specially likely to over-protect them, they make more than the average demand for attention. One could see this most clearly in Case 29 just mentioned. There one could see the difficulty experienced by the child's mother in handling him, and the over-anxiety and subsequent over-protectiveness aroused in her. In this particular case, the response of the mother was a fairly normal one, unlike that which might occur in a more unstable, unself-confident parent.

In Case 3, for example, the parents were not nearly so well equipped to handle the difficulties produced by their much-loved only son. The result was a behaviour problem of the first magnitude with severe asthma-prurigo. In the first case quoted it seemed that the difficulty lay mainly in the personality of the child. In this case both the child and his parents contributed largely to the picture. The difficulty of the one augmented the difficulty of

the other, so that a vicious circle was established from which it was impossible to escape. In a third group of cases the emphasis appears to be upon the environmental factors. Where the patient is an only child, he is likely to be much over-protected from the start. Under such circumstances he may present many symptoms when he is at home and yet be apparently normal when he is away. Here the environment seems all-important and it is easy to overlook how readily the child takes advantage of his over-protection. He finds it particularly hard to break away from a situation in which he gets so much immediate satisfaction of his needs. It gives him the security which his over-anxious nature demands, and also the ability to dominate his environment. But his gain is limited and the ultimate loss far greater, for he loses his freedom. The situation thus represents a pathological solution of a problem which is created partly by his own personality, partly by his environment. A gratification of his immediate needs is obtained at the expense of other and ultimately more important ones. This is the price of all partial and incomplete solutions of psychological difficulties. In this case, when the child has made himself the centre of the picture and has completely dominated his family, he has also, paradoxically, completely lost his freedom. His parents watch over him uneasily and unwittingly thwart his smallest attempts to discharge his aggressive impulses along healthier lines. Moreover the child is particularly unfitted to withstand such restriction and thwarting. Beneath it he rapidly becomes tense and irritable.

So the picture is completed, and one can see the full-fledged personality-type emerge, with its origins partly in the environment and partly in the child. Enough separation of these origins can be made to enable one to realize that both factors have to be considered. On the evidence it is reasonable to suppose that this personality-type is not entirely secondary to the environment. From the shifting pattern of personality in action, constantly modified as it is by forces from outside, one can pick out certain trends which appear to belong to the essential stuff of which the individual is made. The source of these features must be sought in his original endowment.

The Individual Asthma Attack

It is far easier to observe the individual attack of asthma than to isolate an episodic outburst of irritation. The latter is so much less clearly defined that it is hard to follow the changes which occur. Consequently, in making observations upon the factors which are associated with individual attacks, the bulk of the work has been carried out with asthma. If enough of the variables could be brought under control, asthma would be an excellent symptom to use for experimental purposes. The importance of different stimuli and their relationship to one another could be gauged quite accurately, using the asthma attack as the critical reaction. This ideal state does not yet appear to be within the bounds of possibility, but it has seemed worth

while to make careful records of the period preceding each asthma attack, along psychiatric lines.

Adolf Meyer has laid stress upon the importance of the 'complaint in its setting' for the understanding of psychiatric problems. A careful study of all the factors present during the period leading up to the onset of the 'complaint' helps one greatly to obtain an understanding of the problem. Accordingly, wherever possible, each fresh asthma attack in these patients has been treated as a new 'complaint', and the factors involved have been studied afresh. This is not possible unless the patient or relative is interviewed quite soon after the attack. When many attacks are occurring, the salient features of each soon fade into oblivion. Thus not all the attacks which occurred during the period of observation have been recorded in detail. Of those which have been studied, some were reported in much more detail than others. In all it has been possible to observe 43 attacks of asthma in this manner, occurring in 14 individuals in the course of the year.

It is necessary to consider in what manner the asthma attack may be related to the psychogenic factors found. There are clearly three immediate possibilities: (1) the attack may be quite independent of any psychological difficulty which is present; (2) it may partly depend upon such difficulty; (3) it may completely depend upon it. All the evidence which has been gathered so far points to the casual importance of psychological factors. This does not mean for a moment that all asthma attacks are psychogenically determined. Nothing would be farther from the truth. But in many cases the relationship of the presence of psychological difficulties to asthma attacks has been clearly demonstrated. Such difficulties, as was stated above, may be partly or wholly responsible for the attack. In either case their mode of operation must be similar, and it must be comparable to that seen in the production of other somatic symptoms along psychological lines. The possible mechanisms have been stated by Gillespie in a recent paper. 'Psychoneurotic symptoms . . . may be regarded: (1) Simply as the expression of a mental conflict or state of uneasiness. In this case the choice of the presenting symptoms may depend upon constitution or accident. . . (2) As peculiarly symbolic of the nature of the conflict—as when, for example, a feeling of suffocation is a symptom of psychoneurotic form and represents a memory of some childhood incident or fantasy such as the experience of being smothered. (3) Teleologically—for instance, as an expression of a means of escape or as a desire for sympathy. . . (4) As a conditioned reflex when the conditioned stimulus is itself either of an obviously psychological order, or, although apparently of a physical order, depends for its effectiveness on psychological associations.'

Results

When the asthma attacks which have occurred in these patients are considered they are found to fit into various parts of this category. Table III

shows a general survey of the incidence of the 43 attacks which were studied in relation to psychogenic and other factors. In this table the following notation is used.

Column 1 gives the number of the case in which the attack was studied. Column 2 gives the number of the individual attack in the case. Column 3 gives the apparent psychogenic factors. It is divided into two parts: (a) predisposing factors and (b) precipitating factors. Under the latter heading are included only definite psychological traumata occurring shortly before an attack. In section (a) the following notation is used: + signifies the presence of personality or environmental difficulties in the case which have been operative over a considerable period; ++ signifies the presence of difficulties which, although they cannot be classed as precipitating traumata, yet have operated acutely over a fairly short preceding period. In Column 4 the apparent psychological mechanism is included where it seemed at all clear. The numbers 1, 2, 3, and 4 refer to the numbered list of possible mechanisms given by Gillespie and quoted above. Thus the number indicates that the symptoms appear to be: 1, the general result of a psychological difficulty; 2, specifically complex determined; 3, teleologically determined; 4, the result of a conditioned reflex. In Column 5 is shown the time relationship between the apparent precipitating trauma and the attack. In Column 6 apparent somatic factors are included where present.

It may be argued that one has no right to pick out special sets of facts in this way and relate them to subsequent asthma attacks. The justification which is claimed for this is the relationship which has been deduced from other sources. Not only have psychological difficulties been demonstrated with great frequency in these cases, but the coincidence of clinical improvement with removal of the difficulties has also repeatedly been found. Thus this rather arbitrary selection of data becomes reasonable.

When one studies the table the frequency of various factors can be seen. In the great majority of the cases there are predisposing factors of a kind which have operated over a considerable period. These are sometimes almost lifelong in character, sometimes they are of a more immediate and pressing kind, not, however, so sudden or acute as to constitute a precipitating trauma. An example of the first type is the lifelong difficulty of the over-protected only child. The second type of difficulty may be illustrated by Case 7. In this child there was a recurrence of symptoms lasting for a few weeks at a time when his mother became pregnant for the third time. She was very anxious not to have another baby, and there were repeated quarrels between the parents and an atmosphere of tension in the home. With the acceptance of the situation by the parents, the child's condition again improved.

In 20 out of the 47 attacks recorded there appeared to be a precipitating trauma in the shape of fright, anger, or anxiety. In one case marked anticipation of an attack seemed to precede the outbreak of symptoms. In

TABLE III

Case.	Attack.	Apparent psychogenic factors		Apparent psychological mechanism.	Time relationship to precipitating factors.	Apparent somatic precipitating factors.
		(a) pre-disposing.	(b) pre-precipitating.			
1	1	+	+ Temper tantrum	1	6 hours	—
	2	+	—	—	—	—
	3	+	—	—	—	—
	4	+	+ Temper tantrum	1+3	6 hours	—
	5	+	+ Temper tantrum	1	4-6 hours	—
2	1	+	—	1+4	Rapid	+ Fish sensitive
	2	+	—	1+3	—	—
3	1	+	—	1	—	+ Catarrh
4	1	+	+ Fright	1	12 hours	—
	2	+	—	1	—	+ Catarrh
5	1	+	+ Anxiety	1	10 hours	—
	2	—	—	—	—	—
7	1	+	+ Fright	1	6-8 hours	—
	2	+	+ Fright	1	6-8 hours	—
	3	+	—	—	—	—
	4	+	+ Fright	1	8-12 hours	—
	5	+	+ Fright and anger	1	6-12 hours	—
	6	++	+ Fright and anger	1	12 hours	—
	7	+	+ Fright and anger	1	6 hours	—
	8	+	+ Anxiety	1	12 hours	—
	9	+	+ Anxiety	1	6 hours	—
	10	++	+ Anxiety	1	6 hours	—
	11	+	—	—	—	—
	12	++	—	1	—	+ 'general malaise'
	13	++	—	1	—	—
	14	++	—	1	—	—
	15	++	—	1	—	—
	16	+	—	—	—	—
	17	+	+ Anxiety	1	12 hours	—
11	1	++	—	1	—	Seasonal
12	1	—	+ Excitement	1	8 hours	—
	2	—	+ Suggestion and anticipation	4	Indefinite	—
13	1	+	—	1+3	—	+ Catarrh
14	1	—	+ Anxiety	1	8 hours	—
15	1	+	+ Anxiety	1	4-6 hours	—
21	1	+	—	—	—	+ Throat infection
	2	+	—	—	—	+ Throat infection
	3	++	—	1	—	—
	4	++	—	1	—	—
22	1	+	—	—	—	+ Catarrh
30	1	+	—	—	—	—
	2	+	—	—	—	+ Catarrh
	3	+	—	—	—	—
	4	+	—	—	—	+ Catarrh and dyspepsia
	5	+	—	—	—	—
	6	+	+ Anxiety	1	Indefinite	—

20 attacks it was possible to study the time-relationship between the psychological trauma and the onset of the attack. In all cases the interval was quite a long one, and in none of them did an actual asthma attack follow immediately upon a disturbance. In one or two instances a severe fright was followed by an exaggerated breathlessness, but this could not be called asthma, though it was sometimes regarded as such by the patient and his relatives. The most frequent time interval was 4-8 hours, in one or two cases an attack of asthma followed as much as 12 hours after a severe disturbance. There did not appear to be any direct relationship between the degree of disturbance and the time interval which elapsed. These findings are of interest in view of the general impression that when an asthma attack is related to a traumatic experience, it is likely to follow immediately upon its heels. One of the cases quoted most widely in support of the psychogenic origin of certain asthma attacks, is that of Trousseau. He observed a patient who was sensitive to roses. On being handed a wax rose she immediately developed an attack of asthma. This supposedly classic example is in fact an uncommon one if the results of the present work are representative. It is uncommon, moreover, in the mechanism by which the attack was brought about, for it is a clear example of Gillespie's fourth group, the 'conditioned response'.

Turning now to a consideration of the mechanisms involved, one finds that in a very large proportion of the cases the relationship between the symptoms and the psychological difficulties appeared to be a general one. In not one single case did the attack seem complex-determined or peculiarly symbolic of the nature of the conflict in the patient's mind. It may be argued that the methods used were too crude to uncover such a relationship between symptom and difficulty. Yet, on the other hand, many psychological symptoms are clearly and demonstrably complex determined in a way that can be understood from a detailed consideration to the history of the case. No such mechanism came to light in the study of these cases. This does not mean that such a relationship is non-existent between the attack and the predisposing factors. In certain cases it may exist, but not one such was found in this group, so that it appears to be rare. The teleological factor was very difficult to assess; in a number of cases there were personal advantages which the patient could derive from the attack, but it was not always possible to see how far this played a causative part. In none of the cases did this appear to be the sole or even the most important mechanism; on the other hand it is reasonable to suppose that it was an additional factor in quite a number of them. This is in line with common experience of the aetiology of psychological symptoms.

Numerous examples could be quoted to illustrate the points mentioned. Case 1 was a child with general environmental difficulties whose attacks of asthma were several times preceded by outbursts of anger. In this case the considerable time interval makes the importance of the teleological factor seem less likely. Case 2, on the other hand, definitely used his prurigo to

attract his parents' attention, and would constantly scratch himself in their presence. It seems possible that his asthma attacks also may have served the same purpose.

In one case only did the symptoms appear to arise as a conditioned response; this was a boy (Case 12) who habitually had asthma at the weekend. In many cases this would point strongly to factors in the home of a disturbing character to which the patient was not so much subjected during the week. In this case no such factors could be found, but the patient appeared to anticipate his attack with great concern and absolute certainty. It was interesting that suggestion under hypnosis completely abolished the attacks, a procedure which is seldom of much permanent help to asthmatics.

It will be noted from the table that in many cases different factors seemed to be operative at different times. In some there appeared to be a physical basis for one attack and a psychological basis for the next. In others the two sets of factors seemed to combine to produce an attack. A beautiful 'experiment of nature' occurred with one of the children (Case 2). At home, in a difficult environment, he was sensitive to fish and certain nuts. His sensitiveness took the form of an outbreak of prurigo when he came into contact with these substances. On one occasion he was given a chip potato that had been fried with fish; the result was an immediate outburst of urticaria and prurigo. The element of suggestion cannot have been important here since he was not aware of the presence of fish. When he was away at a convalescent home, happy and free from anxiety, he was able to eat fish of all kinds with impunity. Some time after his return, however, he was again unable to eat fish. Another observation made upon the same case shows that the factor of suggestion was not the important one. It has been stated that he was also sensitive to certain nuts. The family believed that all kinds of nut were involved, and when one day he bit into a walnut accidentally, there was great consternation. He was delighted to find that he did not become ill, and cried out that he was much better now and could eat nuts. At a later date he ate a Brazil nut with the immediate return of symptoms. It was found that he was sensitive to Brazil nuts and not to walnuts. If suggestion had played a large part in this child's attacks, he would surely have developed prurigo when given the walnut, since he was certain that this would occur.

This case illustrates what one believes to be a very important point, it shows how a physical factor may lead to symptoms when other factors of a psychological kind are present. The significance of a convalescent home to this child was not that of a place where he was more fit but a place where he was more free. This psychological meaning of convalescence is one which has been demonstrated many times. At home with an over-anxious, over-protective mother he grew more and more tense until a variety of stimuli, psychological or physical, would fire off an asthma attack. Away from home, in a free, unanxious atmosphere, the child was at ease, and the same stimuli failed to produce any effect.

It is interesting that an observation of a similar type was made by Trousseau upon himself. He noted that the combination of an outburst of anger against his coachman, and the presence of oats and other dust in his stables produced an attack of asthma of very great severity. The same dust, when he was not in a state of emotional tension, was capable of producing a mild attack but not one which in any way approached the severity of the other.

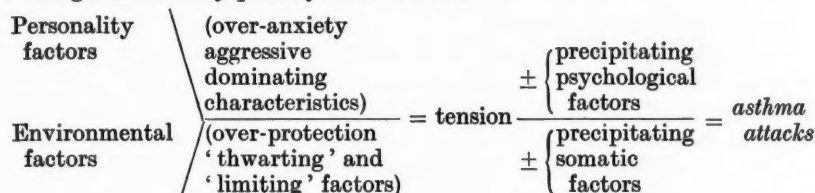
Discussion of Observations

The great majority of the attacks of asthma occur in relation to psychological difficulties in a general way. They are not the product of complexes, they do not express symbolically an unconscious conflict. This is a point which one would like to emphasize very strongly since it is the key to the understanding of the whole relationship of asthma to psychological difficulties. In a few cases other mechanisms may account for the attacks. They may be teleologically determined or they may arise as the result of suggestion. Occasionally they may prove to be complex-determined, but this is apparently the exception rather than the common happening.

Let it be said then that asthma bears a general relationship to the psychological factors. Is it not possible to carry that statement farther? One believes that it is. The children of this group have been shown to be intelligent above the average, they are over-anxious and show many characteristics of an aggressive dominating type. In their environment one has found over-protection and over-anxiety. Under circumstances such as these, one has seen a rapid development of tenseness and irritability. This has been shown not only in the home but also in the clinic when, for any reason, the child has been thwarted or frustrated. When he is tense he develops asthma with much greater readiness either as the result of precipitating psychological traumata or of physical agents. When he is away from a difficult environment, he loses his tenseness and irritability, and at the same time he is able to withstand far greater traumata of all kinds. Thus it appears that the less obvious factors in the background may really be the most important in determining whether or not an attack shall occur. A fright on the one hand, or an allergen on the other, may play the more dramatic and more obvious role, yet for their success or failure they may depend absolutely upon the general life-situation of the individual. If he is living in a state of tension, to which his personality makes him especially prone, then he is likely to have an attack under the smallest provocation. If he is not in this condition he may withstand many stimuli.

This relationship is of great theoretical and practical significance. Unless it is fully understood, the role of other factors may be misinterpreted. A stimulus which is a precipitating factor may be assumed to play the entire causal role in the production of the attack, whereas, in fact, it may be only responsible for firing the trigger which sets off the attack. Thus the most baffling variations in the power of various stimuli to produce an attack may

occur. From the observations which have been made, it appears that an immediate precipitating factor may not even be necessary. In many cases the general difficulties in the background are sufficient to cause a series of attacks. The relationship of asthma to the psychological factors may then be diagrammatically portrayed as follows:



The importance of the occurrence of this 'tension' is very great. By the more intelligent parents and the older patients it is often recognized and described. It may then be termed fatigue, but on analysis such fatigue usually turns out to be, not exhaustion, but tension. For example, an individual who struggles for a long time unsuccessfully with a problem or difficulty feels fatigued and may develop symptoms of asthma-prurigo. The successful solution of the problem banishes the sensation of fatigue, and the symptoms disappear. His tension is in fact relieved. The avoidance of such tension constitutes an important part of the hygiene of the life of the asthma-prurigo subject.

Results of Treatment

One important point yet remains untouched, namely, the results of treatment in these cases. It has been shown in previous work that a change of environment will produce a complete remission of symptoms in many cases. Furthermore, the essential features of the change are the removal of psychological stresses and not an alteration of physical conditions. But it is neither practicable nor advisable to remove every child who suffers from asthma-prurigo to some gigantic and permanent holiday camp. Before it is possible to speak of successful psychological treatment it is essential that the child be able in most cases to continue to live an ordinary life. There are obviously two ways in which this may be brought about; firstly, the environment may be modified so as to render it compatible with the child's personality; secondly, the child may be modified so that his personality no longer clashes seriously with the environment. In practice both these things are attempted, the first by enlightenment and re-education of the parents, the second by direct treatment of the child.

Before treatment is begun, it is necessary to survey the case quite thoroughly to ensure that no physical factors are being overlooked. Next, it is necessary to consider the psychological factors in the case. Here, again, there must not be an exclusive attention to the type of difficulty which has been so frequently revealed. In certain cases other factors will be of equal or greater importance, and the known tendency towards these particular

difficulties serves only as a guide. In this respect this 'known tendency' is of the greatest value, for it enables one to make a preliminary survey of the case history, and to pick out what appear to be precipitating factors. The bewildering variation in the production of attacks by different stimuli can be more clearly understood, and the relevant causal factors can be more rapidly brought under control. Thus, for example, the importance of a sudden fright in the production of an attack will not be over-estimated in relation to the underlying tension which may exist. It is in this way that any frequent correlation of observations is of value in medicine. No syndrome is to be regarded as a fixed entity which always occurs in a certain form, it is rather a collection of data which are found together so often that when one appears it is worth while to make a special search for the rest. The observations upon asthma which have emerged from this group of cases are to be considered in this fashion. The treatment of the cases cannot be reduced to a standard formula, each case must be dealt with upon its own merits. A few examples of the type of treatment given are recorded here in order that these points may be made clear.

Case 4. This 5-year old boy was over-active, aggressive, and very dominating in his behaviour. At home he was much restricted by his mother partly because he was her only son and partly because she and the father were over-anxious, highly strung people. He was not allowed out to play with other children, and when they were invited to the house he did not get on well with them. He was not allowed to make a noise at home, since his father was on night duty and slept during the daytime. The problem in this case was evidently one of arranging a more psychologically healthy mode of life for the child. He was allowed to go to school in spite of the risk of asthma attacks, and the mother was persuaded to give him much more freedom. The result was a marked improvement in his symptoms. He did not cease to be an aggressive dominating little boy, but with proper outlets for these characteristics among other children, he ceased to be seriously irritable and bad tempered. In this case the only treatment given directly to the patient was some reassurance and encouragement that he was really quite a healthy normal boy and not an invalid as he had been educated to believe. It is important to note that this treatment occupied only two interviews of less than an hour each. As soon as a detailed history had been obtained, it was possible to see what facts were likely to have a bearing upon the problem and to give the mother constructive advice in the handling of them. The improvement became immediately evident and was maintained satisfactorily. Not all the problems encountered are as simple as this one, but under such circumstances the psychological treatment of asthma is rapid and economical. In the table of results it is recorded that he is still having occasional asthma attacks, although not so many or so severe. It may be argued, therefore, that in this case the treatment was not successful. But it is equally reasonable to suppose that the problem was not entirely a psychological one, indeed it almost certainly was not. A modification of the psychological difficulties produced marked relief, but there were other factors which have not yet been brought under control.

Case 17 is an example of a rather older boy (age 12), also an only son. The parents were persuaded to let him have plenty of freedom and inde-

pendence, and to overcome their marked anxiety and over-protectiveness towards him. But he still remained over-anxious and unself-confident. His chief difficulty was that he could not excel other boys at school, and he would spend hours at home struggling and worrying over his homework. It was arranged that he should come regularly once a week for psychotherapy, and his difficulties were discussed with him during a session in which play and conversation were intermingled. The result was a gradual but satisfactory improvement, and he is now free from symptoms and a much more normal 'out-going' boy.

Many other cases could be quoted in detail showing the type of procedure adopted, but the difficulties which were found in individual cases have already been outlined, and the treatment consists in a modification of these difficulties where it is possible. The results obtained are shown in the end columns of Table I.

In estimating improvement a series of + signs is used in relation to the same notation which was employed in the first part of the Table. There, it will be remembered, symptoms were grouped as frequent (or constant in the case of prurigo), periodic, or occasional, and severe, moderate, or mild. A shift from one of these groups to the next one above it is indicated by one +, a case which moves from the group of 'frequent severe' to that of 'occasional mild' is therefore given a notation of 4+. 'Absence of symptoms' is regarded as next in line to 'occasional mild', and for this one more + is added. Thus maximum improvement is 5+. Changes in the reverse direction are indicated by a - sign. It was not felt to be justifiable in the case of asthma to award the full number of + signs for cases which were free from symptoms, since such freedom might be quite intermittent and the period of observation in no case was more than one year. Where there has been no asthma for a period of six months or over a double plus sign (++) has been used to indicate this fact, all intermissions of less than six months have been grouped as 'occasional'.

The notation used varies slightly from that which was suggested recently by the Asthma Research Council in estimating improvement in asthma. It was felt that these groupings, in these particular cases, brought out more clearly the change or lack of change made by the patient during the year.

Of the 22 asthmatics, 7 had been free from symptoms for a period of 6 months or more, 5 showed an improvement of 2 to 4+, 4 showed an improvement of 1+, 3 were not better and 3 had not been reviewed at the end of the year. Of the 17 who suffered from prurigo, with or without asthma, 5 were free from symptoms at the end of the year and had been so for several months. In addition to these, 3 cases showed an improvement of 3 or 4+, 5 showed an improvement of 1 or 2+, and 4 were not better.

It is not desired to lay stress upon the numerical value of these figures. An exact assessment of clinical improvement could not possibly be made in cases which were under observation for a period ranging from a few months to a year. Furthermore, in the treatment of them no attempt was made to eliminate all other types of therapy. Such a step would scarcely be justified

in view of the partial role which is played by the psychological factors in asthma-prurigo. It is necessary to recall the fact that the cases were largely unselected, and that in some of them the psychological factors played only a small part, whilst in others they appeared to be very important. As far as possible the introduction of different methods of physical treatment during the period of observation was avoided, and in many cases the treatment was carried out solely in the Department of Psychological Medicine. The one conclusion that it is desired to emphasize is this: that psychological treatment is in some cases able to prevent the attacks completely, and in many others it is able to assist materially the known physical remedies.

Summary

A certain group of children with asthma-prurigo has been studied. In many of them are found special personality features and special environmental difficulties which are closely related to the attacks. In those which have been studied some have followed very closely the typical findings, others have done so to a less extent. It is believed that the facts as they have been presented may help to clarify the psychological understanding of asthma and particularly to co-ordinate the physical and psychological aspects of treatment.

I should like to express my thanks to Dr. R. D. Gillespie for permission to publish the cases and for much helpful advice and criticism, and to my colleagues in the Department of Psychological Medicine whose co-operation has made the work possible. The work has been done under grants from the Rockefeller Foundation and the York Trust.

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ISOLATED UNCOMPLICATED DEXTROCARDIA¹

By D. S. STEVENSON

With Plates 11 to 14

THIS condition is so uncommon and yet raises points of such interest both cardiologically and embryologically that it justifies recording. There are few reports of true cases in the literature, and not all of these complete with X-ray and electrocardiograph findings.

The patient whose case is here reported is alive, doing active work and is comparatively well. The dissection is one of Professor Allen Thomson's and was reported previously (1), but appears to have been lost sight of in the literature (2, 3, 4). I had the good fortune to rediscover the mummified specimen while looking over aortic abnormalities in the museum of the anatomy department of the University of Glasgow and to find the report after a considerable search through various Journals. The similarity of the findings in the dissection to those in my living case is very remarkable and aids greatly in their interpretation.

Dextrocardia has been recognized since the earliest days of medical investigation (5), but is commonly a part of a total *situs inversus*, of which many cases are on record. Some are recorded of dextroposition without visceral transposition, from various causes, such as eventration of diaphragm and consequently with the cardiac apex still to the left and no electrocardiographic alteration. These cannot be termed true dextrocardias. Other cases are on record of visceral without cardiac transposition.

Isolated uncomplicated dextrocardia appears to be the most suitable name for the condition in the case now to be described, this name being partly taken from the exceedingly complete paper of Lichtmann of New York (2). By the term 'isolated' is meant that the heart alone is completely transposed without other complete visceral transposition. The terms 'complicated' or 'uncomplicated' are used to mean with or without cardiac malformation in addition, and in my case uncomplicated must be applied. That the condition is congenital must be obvious, and this addition to the name unnecessary. Some embryological points will be discussed later.

Full clinical investigation of the patient has been made from time to time over a period of nearly four years and any alterations noted. Electrocardiograph tracings have been repeated and a series of X-ray photographs taken to clear up certain points. Screening has been of much value for observing movements.

The Clinical Case

J.P., 42 years, married, and occupied as a warehouseman, was admitted to the wards of the Western Infirmary, Glasgow, under Dr. James Carslaw

¹ Received June 18, 1937.

on July 25, 1933, complaining of shortness of breath and of a sensation of abdominal fullness after food. These two symptoms had been increasing gradually for the past six years. He also had some cough with mucoid sputum, and had occasional palpitation which he felt to the left of mid sternum. He was dismissed well after one month in hospital, the congenital deformity being recognized and followed up later.

The only illnesses in his past history were that he had had attacks of breathlessness—1912 in South Africa, 1928 at home, these requiring two minor nasal operations—and that he had a mild pleurisy, without effusion, while serving in France in 1917. He remembers no serious illness during childhood. He was not incapacitated during the world war, throughout which he served—attaining the rank of Captain in the Machine Gun Corps.

The family history in such cases is of importance, and I have questioned him in detail about this. He is a Jew and can trace his paternal descent over two centuries back to the town of Memel. He knows of no twin pregnancies on his father's side. There were twins a generation back on the mother's side. He was not a twin and was not injured at birth. The mother and father were half cousins so that consanguinity can be considered. His mother informs him she had no fright, injury, or other untoward event during his intra-uterine life. He has four brothers and two sisters all alive and believed to be normal anatomically—one brother is a mental defective—the remainder are well. His wife has had three children, each singly. One is alive, normal and well, the other two died of infections in early life—they were believed to be normal anatomically. So far as he is aware there are no other cases of congenital abnormality of any kind in his relatives. His father, mother, and their family were averagely tall.

He is of less than average height and weight—5 ft. and 7 stone—does not look Jewish, is mentally alert, and shows no cyanosis, clubbing of fingers or other obvious abnormality. On examination, standing naked, the principal points of note are that he is flat chested, more marked on the left side as an anterior depression, and that his left testicle hangs lower than his right. His nutrition is fair and muscle tone good. No developmental abnormalities are seen, e.g., of sternum, of penis, of ears, of fingers, or of toes; nor are any present in palate, lips or face. Posteriorly he has a clump of hair over his sacrum but no spina bifida occulta: he is right-handed and right-eyed (shooting, &c.).

Circulatory system. The apex beat is normal in type but is in the fifth right intercostal space 3 inches from mid sternum. No abnormal pulsation is seen in the neck vessels or in the suprasternal fossa. No thrill is present. The cardiac dullness is: upper border at third rib, outer border $3\frac{1}{4}$ inches to right of mid sternum, mesial border $\frac{1}{2}$ inch to right of mid sternum. Sounds are pure and of good quality—an occasional extra systole is present at rest, but disappears on exertion. The blood-pressure left arm is 140/85—after deep breathing 130/85: right arm 135/80—after deep breathing 120/75. On a later date, left 105/70, right 115/75. Repeated observations were made to try to define on which side the abdominal aorta was pulsating, but a rigid abdominal wall made these unsuccessful.

Respiratory system. Some flattening of the left thorax is present anteriorly. Movements are equal and average. There is no dullness to percussion. The breath sounds are vesicular throughout, with a few rhonchi.

Alimentary system. The tongue is rather furred, the teeth fair, the throat

normal excepting a high arched palate. He is tender in the epigastrium, and has a sensitive abdominal wall. The kidneys are not palpable, and splenic dullness is elicited in the left flank. Percussion of the liver outline shows this to extend normally to the right but also unusually far to the left. No abnormality was discovered in the central nervous or in the genito-urinary systems. Ophthalmoscopic appearances are normal. Wassermann is negative; blood count and test meal are within normal limits. No occult blood is present in his faeces.

X-ray findings. The heart is in the right side of the thorax and has its apex pointing to the right. The main shadow is of normal form completely transposed, and screening shows the movements of a mirror image dextrocardia with the conus arteriosus in its usual position relative to the arterial ventricle. The shadow of the venous side, i.e. in this case the left, is not of the usual shape, in that where normally a slight protuberance, interpreted as superior vena cava, is noticed, there is a moderately large triangular shadow. Part of this triangle I believe to be the shadow thrown by the superior vena cava and its junction with the venous auricle; the remainder is difficult to interpret, but the large left azygos vein may form a part. Examination of the dissection (vide photograph 4) supports this view.

The aortic arch is seen curving to the right, and oblique films taken from the right and left sides, when the oesophagus was filled with an opaque bolus, show that the aorta and oesophagus are not actually in contact as none of the usual pressure curves are present. The oesophagus also appears to be clear of the venae cavae and of the pulmonary artery—this latter presumably dividing immediately under the right aortic arch. The venous side of the heart is not dilated or it must have displaced the oesophageal shadow.

The type of heart would therefore seem to be that in Mandelstamm and Reinberg's (3) classification No. III—the 'mirror image dextrocardia with a right aortic arch'.

Plates to define the lobes of the lungs are not sufficiently clear to permit of dogmatic statements but suggest the right is trilobed and the left bilobed. The oesophagus passes down just to the left of the midline to enter the stomach through the medial portion of the left half of the diaphragm. This left half shows constantly the higher. The stomach is placed more than usually to the left and there is considerable ptosis. The greater and lesser curvatures run in their normal directions to the pylorus which points to the right. The duodenum is not entirely normal in its curve owing to the ptosed stomach and to the position of the duodeno-jejunal junction. The first part of the duodenum is elongated and passes upwards to reach its normal termination under the liver to the right of the middle line; the second portion is also elongated and descends directly to join the third part which crosses transversely to the ptosed duodeno-jejunal flexure immediately underneath the gall-bladder. The remainder of the small bowel is bunched up in the right iliac fossa. The caecum is in the midline and the large bowel is shorter than normal and practically all placed mesially and to the left. The vermiform appendix defied all efforts to define its site. The renal shadows are clearly seen (unpublished X-ray), the left being definitely the lower.

An attempt was made to define the position of the liver and of the gall-bladder by cholecystography—dye being given by the intravenous route. The gall-bladder is clearly outlined, low down and in the midline with its apex pointing to the left. The liver shadow is difficult to interpret as the lobes could not be defined. The main bulk is mesial but extends out to both

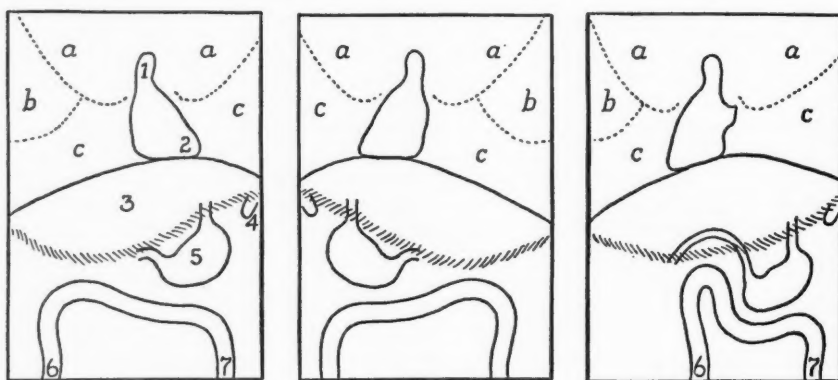
sides of the thorax, the left half of the diaphragm-liver shadow being constantly the higher.

Most of these points are demonstrated in the published photographs.

Electrocardiographic examination. This was done on a number of occasions, with conventional voltage for emphasis, with usual leads and with arm leads reversed. The graph is that of an uncomplicated dextrocardia (6)—lead I showing reversed direction of all deflections, lead II becoming equivalent to lead III, and lead III to lead II. With the arm leads reversed there is a return to the normal graph.

It is, I think, clear that this is a case of uncomplicated dextrocardia and that it also comes under the category of isolated, as there is no corresponding transposition of the abdominal viscera (vide diagram). The cardiac apex is proved to lie to the right, clinically and by X-ray. There is no evidence of pulmonary disease nor of diaphragmatic abnormality. The aortic arch shadow is seen curving to the right, the cardiac chambers are normally related (3) to each other and electrocardiograph tracings show the form of true dextrocardia (6, 7). No clinical evidence is present of valve leaks or of patent foramina or ducts. The case would therefore appear to come under the heading of an 'ideal mirror image' (2) isolated dextrocardia.

The other abnormalities present are the mesial position of the gall-bladder and caecum and the shortness and position of the colon. The liver is also abnormal and appears to be an almost symmetrical mass while the elongated first part of the duodenum terminates in a normal position for an untransposed liver. The higher left half of the diaphragm suggests transposition, and this is probable in order to establish uncomplicated connexion with the transposed venous side of the heart. A consideration of these in addition to dextrocardia may prove of some value in theorizing as to the possible aberrant mechanism which determines dextrocardia.



Normal.

Complete
transposition.

Isolated
dextrocardia.

1. Aorta.
2. Heart apex.
3. Diaphragm + liver.

4. Spleen.
5. Stomach.
6. Caecum.
7. Large bowel.

- a } Lung lobes.
- b }
- c }

The Museum Specimen

Professor Allen Thomson's report, which is accompanied by a drawing, is headed :

'Dissection of a case of lateral transposition of viscera of thorax and abdomen in a man.'

The following are extracts which contain the main features :

'Man, 48 years : well built—above average size. Marble cutter. Nothing known of history except rheumatism in early life. Eight years ago pleurisy. Not known whether right- or left-handed. Died in Glasgow City Poor House, February 4, 1853, after one week's residence.'

'*Clinical* : Dullness left base—much muco-purulent sputum. Apex beat to right and cardiac sounds best heard to right. Urgency of illness precluded much investigation and right heart supposed to be due to displacement by left empyema.'

'The cadaver was sent to the Anatomy Department, Glasgow University, where it is preserved, and where the photographs were taken for me.'

'Through the kindness of Dr. A. S. M. Macgregor, M.O.H., Glasgow, I was able to have a search made of the old records and found the name of the man, initials J. N., that he was born in Nova Scotia, and that he had a wife and two sons in England. Should heredity be an important factor it is not unlikely that further cases will bear the same name. I have not attempted to get Nova Scotian records as to his mother's name.'

'Measurements of the bony skeleton suggest that he is likely to have been of more than average height—probably six feet.'

Thorax. The heart points to the right with the apex to the right; the arterial ventricle is not seen on antero-posterior view as it is all placed posteriorly and to the right. The aortic arch passes over the right branch of the trachea and the aorta is well clear of the oesophagus until this lies immediately in front of the descending aorta which passes down in front of the vertebral bodies. The venous auricle is to the left where it is joined by the descending vena cava superior, and by the ascending vena cava inferior. The venous ventricle is anterior and to the left side and from it the pulmonary artery winds round under the arch of the aorta, there forming its right and left branches. The remains of the ductus arteriosus pass from the aortic arch down to the right branch of the pulmonary artery. No remains of the primitive left dorsal aorta are seen.

Abdomen. The left half of the diaphragm is the higher. The stomach is to the left and its splenic attachment can be seen there—although the spleen is not preserved. The duodenal curve passes upwards and transversely across the abdomen and then down to join the small bowel where it is bunched in the right iliac fossa behind the large. The caecum is to the left and the vermiform appendix low down in the left iliac fossa. The pancreas had its head to the right and its tail behind the stomach. The left kidney was the lower and the lungs were left trilobed and right bilobed.

The liver here was definitely transposed and—although it is not preserved—is shown clearly in Professor Thomson's drawing. The gall-bladder is preserved, but in the specimen has been attached artificially to the ensiform cartilage. The drawing shows it well to the left, below the large left lobe of the liver.

Comparison of the anatomical findings in this dissection and of the clinical and radiographic in my case shows a remarkable similarity, especially with regard to the heart—a 'mirror image' dextrocardia with the right dorsal aorta functioning (8). The liver in the dissected man's case was transposed, as also were the lungs—these points are difficult to verify in my living case. The stomach and bowels in the dissection are as in my case.

Embryological Considerations.

The work of Spemann and Falkenberg (9) on the Triton larva shows that artificial reversal through 180° of the middle third of the Darmdach—i.e. the dorsal part of the primitive ectoderm and entoderm—down to the deeper layer of entoderm in the gastrula stage of the larva results in complete visceral transposition.

The bilateral symmetry of vertebrates is probably brought about by the elongation of the radial gastrula into a cylinder and the fusion, along the dorsal aspect, of the lips of the gastrula mouth, this fusion taking place from before backwards (10). The active process of gastrulation of course is not clearly visible in the early development of the human embryo but is reflected in a modified and abbreviated form in the formation of the neurenteric canal.

As the mammalian blastoderm becomes folded off from the roof of the yolk sac, the heart forms as two mesodermic tubes, which are separate to begin with. In the human embryo of 2 mm. these have fused and the primitive heart tube has taken an S-bend due to lack of pericardial space; constrictions are already present which will divide off the heart into bulbus aortae, auricle and ventricle.

As the tail fold develops, and the embryo develops in length, the primitive streak becomes applied to the floor of the hind gut and the connecting stalk is displaced forwards. The fore gut passes into the head fold: behind the primitive pharynx it forms the short oesophagus which in turn widens out into the straight stomach dilatation, which soon shows its concave lesser and convex greater curvatures—the lower pyloric end forming the duodenal loop. The stomach then turns over and the duodenal loop is thrown to the right side. The rudimentary liver is formed from a short forward diverticulum from the section of gut between the stomach and the mouth of the yolk sac. The liver grows rapidly and soon occupies a large portion of the abdominal cavity. The intestine is increasing in length and forms the vitelline loop, with a proximal descending and a distal ascending limb. These limbs come together and the caudal extremity which will later be mid colon approximates with the duodenal loop. On the distal limb the rudimentary caecum develops,

and the distinction is made between small and large bowel. Rotation in the long axis occurs and is completed as the umbilical loop enters the abdomen at about the 40 mm. stage. The small bowel becomes displaced to the left under the large, and the large bowel forms an inverted U-shaped loop surrounding the small.

In my present case and in the dissection, dextrocardia would appear to have occurred from the original S-bend of the heart tube having formed in a contrary direction laterally; the arch of the aorta has formed from the fourth right aortic arch and continued into a persisting right dorsal aorta while the left dorsal aorta has disappeared. Cases of this are on record without dextrocardia (8). At about the same time the primitive intra-abdominal structures have formed normally so far as long axis is concerned, but subsequently the normal rotation of mid-gut loop has been incomplete.

The liver has already been referred to as being indeterminate and possibly a symmetrical mass. Transposition appears likely in order to connect with the transposed venous end of the heart and is suggested by the higher left diaphragm; and unlikely, as it is associated with the left-sided expansion of the stomach and the normal right-sided termination of the first part of the duodenum.

There would altogether appear to have been some defect in an early governing mechanism whose concern is the turning of various structures. The order of development is normally heart, gut, lungs. Here the primary cardiac tube turned contrary to its normal direction, the gut attempted to rotate in the normal direction but failed to complete the process, while the lungs are apparently normal—right trilobed and left bilobed.

The governing mechanism theorized would seem to have been absent at first—or functioning in a contrary direction—then to have begun to function when the bowel was rotating and to have developed its normal function when the lungs were concerned. In cases of complete visceral transposition the mechanism has functioned in a contrary or reverse direction throughout development—and in cases of visceral transposition without cardiac to have functioned normally to begin with and to have failed to do so later.

Much further study of these peculiar abnormalities of development will be required before such theories can be more than theories.

The Triton larva work already referred to is of great interest, and it may be that in the earliest stage of human embryo development some similar but incomplete reversal of structures occurs, associated with the governing mechanism; but it does not seem likely that the mechanism is primarily one of altered anatomical structure as this would make the occurrence of these apparent variations in the time of functioning difficult to explain.

Professor Allen Thompson in his remarks discusses the question whether transpositions may be hereditary like many other malformations, but tends to the view that injuries, or other change, in the earliest stage of the development of the germ would appear to be the most likely cause.

A detailed history of the parentage of known cases of transposition would

be most helpful in attempting to clear up the point of inheritance—possibly as a Mendelian recessive.

Summary

1. A detailed description is given of two instances of isolated and uncomplicated dextrocardia, one still alive, the other from a museum specimen.
2. Some views as to aetiology are expressed.
3. It is shown that this form of cardiac transposition is not incompatible with a reasonable span of life and activity.
4. The one man being 5 feet in height, the other about 6, disproves that small stature is constant in this form of abnormality.

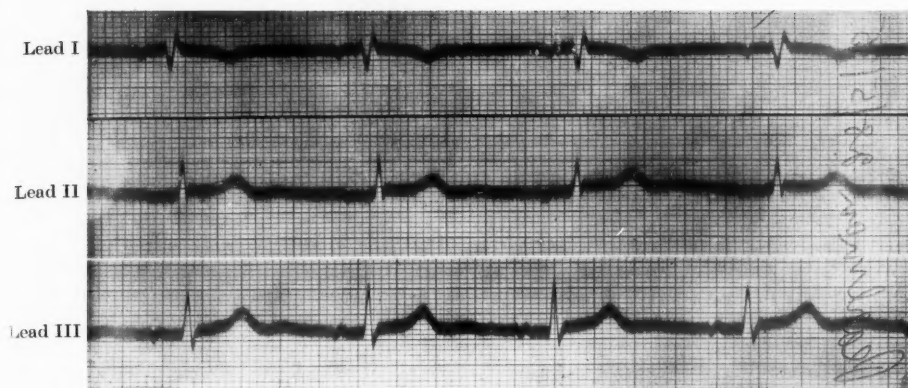
I wish to express my indebtedness to Dr James Carslaw for permitting me to study and to publish the case, to Professor D. M. Blair for permitting me access to the dissection, and to both for much help and kindly criticism. For the photographs I am indebted to Mr. John Kirkpatrick and to him I tender sincere thanks.

A delightful fragment—apparently by the printer's devil—with which Professor Allen Thomson's paper ends, must not be allowed to lie forgotten in the obscurity and dust of more than eighty years. It is:—

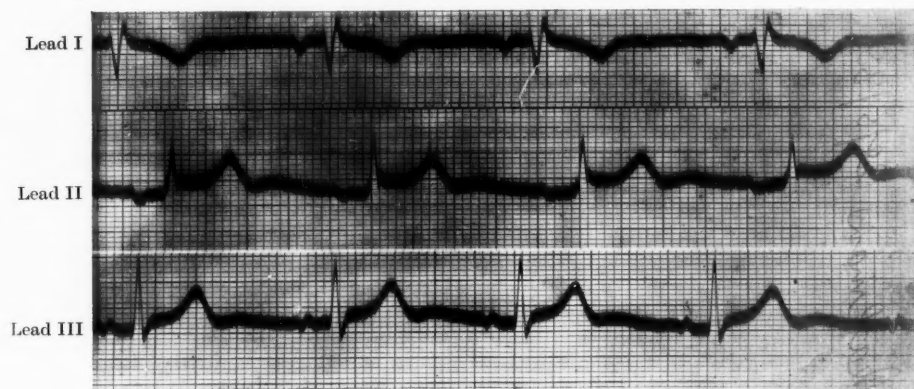
'Once nature a change in man's fabric to try,
His stomach and vitals set entirely awry;
To the left of his belly the liver was found,
And his heart to the right—but all otherwise sound.
Such hodge-podge of structure would hinder, you'd think,
The due courses of blood, of meat, and of drink:
But, strange to relate, they most fitly proceeded
Exactly the way that for health was most needed.
It has often been said of the just and the kind,
That their heart in the right place you're quite sure to find;
And as to our case, I should like to be told,
If this great moral law was still likely to hold.'

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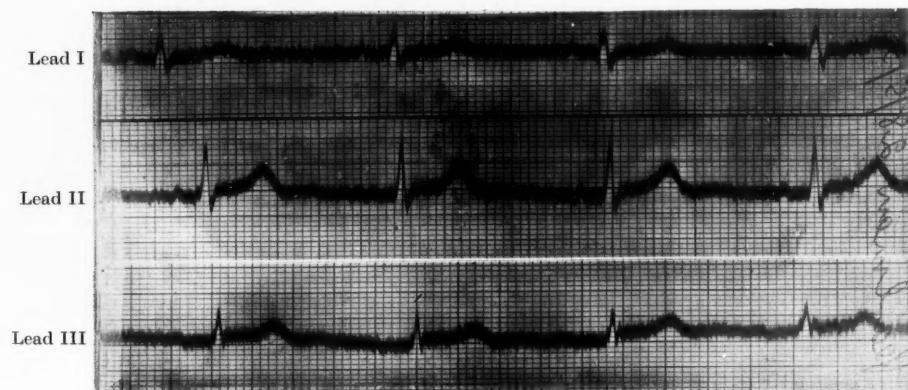
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A. Conventional voltage, usual leads



B. Double conventional voltage, usual leads



C. Conventional voltage, arm leads reversed



FIG. 1

1, Aorta ; 2, Conus arteriosus ; 3, Arterial ventricle—apex of heart ;
4, Venous auricle ; 5, Superior vena cava



FIG. 2

Oblique view. Esophagus filled with barium bolus



FIG. 3

1, Cardiac shadow; 2, Stomach; 3, Duodenal cap; 4, Duodenal curve; 5, Small bowel; 6, Gall-bladder; 7, Duodeno-jejunal junction

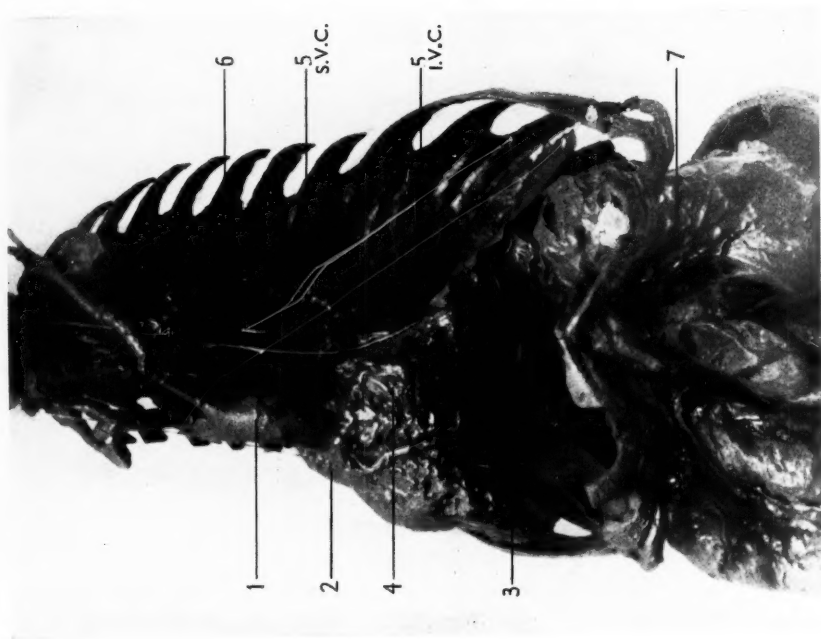


FIG. 4

Direct view, front. 1, Aorta; 2, Conus arteriosus; 3, Apex of heart (arterial ventricle); 4, Venous auricle; 5, Superior vena cava and inferior vena cava; 6, Vena azygos; 7, Stomach

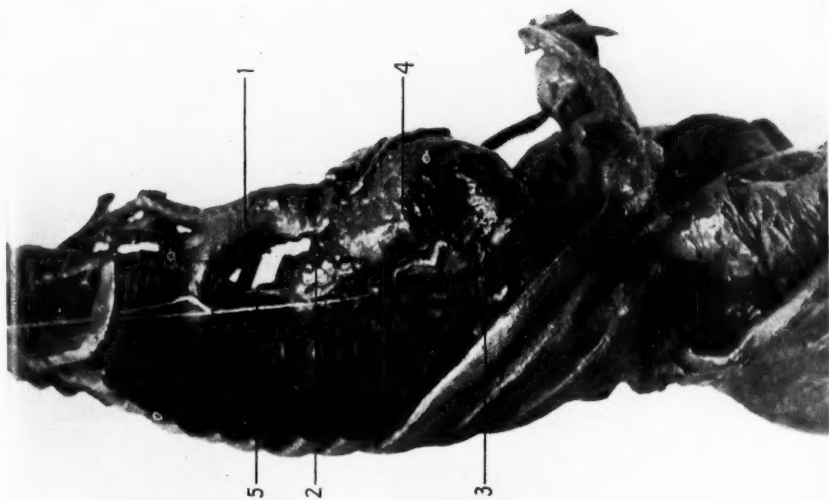


FIG. 5

1, Aorta; 2, Pulmonary artery; 3, Arterial ventricle; 4, Venous ventricle; 5, Remains of ductus arteriosus

HUNTINGTON'S CHOREA IN SOUTH WALES¹

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Introduction

THE chronic hereditary choreas will always serve to attract attention, not only because of the pitiable state of the sufferers, but also because a knowledge of such weaknesses in certain family strains may eventually prove to be the basis of eugenic legislation. The following paper is based on a study of 24 cases of Huntington's chorea—15 of whom have been personally examined and observed by us for a year or more. In addition we have made a detailed genealogical and sociological study of the families concerned, ascertaining as far as possible the incidence of the disease, its mode of heredity, and the constitution, ability, and state of the nervous system in all members, together with an account of their attainments in life. Six family groups have provided the material for this study, and, with one exception, they have been natives of South Wales, viz. the counties of Glamorgan, Carmarthen, Cardigan, and Pembroke. An attempt has been made to trace the original source of the condition in these parts. With this end in view records of County Mental Hospitals and Public Institutions have been consulted, and, in the country districts, general practitioners, older inhabitants, and numerous private individuals have been interviewed.

Although the literature of the last century contains a few early records of the condition, notably those of Rufs (1834), Waters (1841), and Lyon (1863), it was not until 1872 that George Huntington, a physician of Long Island, America, gave the first distinctive account of the disease that has since borne his name. His father and grandfather before him had practised in the same locality and observed the disorder, and it is still interesting to recall the grandson's first acquaintance with the disease as he described it in an address to the New York Neurological Society in 1910.

'Over fifty years ago, riding with my father on his professional rounds, I saw my first case of "that disorder", which was the way in which the natives always referred to the dreaded disease. I recall it as vividly as if it had occurred but yesterday; it made a most enduring impression on my boyish mind, an impression which was the very first impulse to my choosing chorea as my virgin contribution to medical lore. Driving with my father through a wooded road leading from East Hampton L.I. to Agamensett L.I., we suddenly came upon two women, mother and daughter, both tall, thin, almost cadaverous, both bowing, twisting and grimacing. I stared in

¹ Received June 23, 1937.

wonderment, almost in fear. What could it mean? My father paused to speak to them and we passed on. Then my Gamaliel-like instruction began; my medical education had its inception. From that point on my interest in the disease has never wholly ceased.'

Since that time cases have been reported in Europe and elsewhere but relatively few have been observed in the British Isles, where the disease is undoubtedly rarer. In America the New England States have provided most cases, and Davenport and Muncey, Jelliffe, Vessie, and others have made extensive studies of the disease and its inheritance, concluding that the majority have descended from a few individuals who emigrated to Boston Bay in 1630 from Bures, a village in Suffolk, England, sailing in the fleet of the Puritan leader John Winthrop. It is a curious coincidence that the Huntingtons also hailed from East Anglia, leaving Norwich in 1633, only three years after the tainted emigrating families had set sail, both to settle in the New England States. The story of the lives and fortunes of their descendants is admirably told by Vessie, who, studying the public archives of Massachusetts and Connecticut, traced the family for three hundred years. Called 'the magrums' by the early Dutch settlers, it was regarded as an ignominious affliction, inspiring awe among the countryfolk and leaving in its wake a long story of witchcraft, trials, imprisonment, and burning at the stake. Persecution led to isolation, and sympathy to intermarriage, so that there were created exceedingly complex genealogical trees fouled by neuropathic inheritance and consanguinity.

Entres, in Germany, has made similar studies, and, impressed by the monotonously regular mode of inheritance, and the inevitably pitiable state of the sufferers, has advised against the marriage of members of tainted families.

In England, however, the disease is fortunately rarer, and, so far as we are aware, no extensive genealogical studies have been made, although Critchley, in 1934, noted the distribution of the disease in the counties and endeavoured to obtain information which would correspond with the conclusion of Vessie that the disease originally came to New England from Bures in Suffolk.

Symptomatology

Straightforward cases are readily recognized from the main features of the disease, viz. the late onset, the chorea, the mental degeneration, and the hereditary factor. Nevertheless, it would appear that the true nature of the condition is often overlooked. In 1910 Jelliffe recalled that the cases he had seen in English asylums were variously classified as catatonia, dementia, or chronic mania. Allbutt, when he showed a case at Addenbrooke's Hospital in 1918, said that he had only seen three such cases in this country in his lifetime, and Critchley, in 1934, stated that there were then 74 cases under certification in the county mental hospitals of England and Wales. During the present investigation into the incidence of the disease

in South Wales we failed to meet a doctor who had encountered any cases in the locality, and of the 15 cases which we observed personally only two had been previously diagnosed. We feel, therefore, that there must be more cases hidden away among the population generally.

The choreiform movements appear to us to differ in no essential way from those of Sydenham's chorea, although there is some divergence of view on this point. Some have thought the movements slower than those of Sydenham's chorea, and others more rapid. Possibly in some cases they appear to be of wider range with a consequently slower movement and, although the face suffers most constantly, no part of the body is exempt. The face, too, wears a sad expression, giving to the patients an air of similarity. During deep sleep the movements nearly always cease, but the sleep may still be restless and disturbed. In case 14 movements actually persisted at times during sleep, although with less severity. In the late stages of the disorder swallowing is frequently involved, and on several occasions some of the patients have nearly choked. Nurses and attendants realize this and watch them carefully at meal-times.

The mental changes, whether they occur before, during, or after the onset of the chorea, consist of a gradual disintegration of the psyche. The early symptoms are carelessness, slovenliness, peculiarities of behaviour, and a general deterioration of habits. The formerly conscientious and placid individual becomes lazy, aggressive, and loquacious, prone to outbursts of anger and destruction. We have been impressed by the frequency with which relatives have insisted that the patient has developed an entirely new character. The shy man becomes sociable, the considerate vicious, the abstainer intemperate, and so on. It is this very fact that makes prognosis difficult in non-choreic members of affected families, for the occurrence of such personality changes renders the so-called pre-choreic traits unreliable. While the intellect suffers from the onset, with loss of memory, weak judgement, and poverty of thought, it is in the emotional sphere that most changes are to be found. The mood is usually one of depression or suspicion, the stream of thought disconnected and irrelevant, while delusions of jealousy, infidelity, and persecution frequently result in acts of assault. Excitement and confusion may be present, but euphoria, grandiose ideas, and hallucinations seem to be rare. In each family studied the same story of emotional instability, mistrust, and violence, with their attendant tragedies, was obtained with monotonous regularity, as is well shown in the case histories. That there is any particular form of insanity peculiar to the choreic patient seems improbable. The manic-depressive form outlined above is by far the most frequent, but cases have been recorded, usually in older patients, in which simple dementia only occurs. A schizophrenic picture has also been recorded in some cases, notably by Oppler (1933).

Davison (1936) has reported the presence of a dense gliosis in the occipital lobes of eight cases of Huntington's, and arteriosclerotic choreas in addition to the usual neural structures involved in the disease. A history of visual

hallucinations was not obtained in any of his cases and perimetric studies, so far as could be obtained, proved unsuccessful in showing any alteration of the visual fields. We have been unable to produce any satisfactory perimetric charts owing to the choreic movements, but in Case 19 we noted the occurrence of visual hallucinations from time to time.

The average duration of the disease is between ten and fifteen years, the last years frequently being spent in a bedridden helpless state of extreme dementia. In the majority, death takes place from exhaustion.

Differential Diagnosis

Sydenham's chorea is rarely of chronic progressive type and is not accompanied by gross mental changes, although the movements may persist as hysterical mimesis. Senile chorea may closely simulate Huntington's chorea, but usually differs, not only in the absence of the hereditary factor but also in its benign course, the frequent absence of mental degeneration and the occasional tendency it shows to recovery, and in the fact that it rarely commences before the age of 35 years. The odd tics, habit spasms, and incoordinated jerks of old people and the occasional occurrence of chorea in a hemiplegic limb must also be differentiated. The dementia of general paralysis shows certain resemblance to that of Huntington's chorea and may cause confusion if the movements are slight or if the paretic shows signs of chorea, as happens occasionally. But the rare coexistence of general paralysis and Huntington's chorea, as recorded by Lowrey and Smith (1918), should be remembered. Post-encephalitic chorea need not lead to much difficulty, as the history of encephalitis and the absence of the hereditary tendency make diagnosis relatively simple.

The Hereditary Process

The known facts of inheritance can be stated categorically. The disorder is transmitted directly by both sexes and the hereditary factor behaves as a simple Mendelian dominant. Both sexes are liable to the disease, but reports are not in agreement as to the preponderance in one or other sex. Members of either sex may transmit the disease, again without proved bias. The disease is said never to skip a generation; the facts on which the opposite view was based have not been generally confirmed. It may appear to miss a generation however, if a tainted member dies before the onset of the disease. Such an occurrence is illustrated in the second and third generations of family B of our series. In the former an apparently healthy woman died in her thirty-fifth year in childbirth, but two of her surviving children acquired the disease. A third child was killed in an accident at the age of 25 years, yet two of his three children became choreic. Nevertheless, Davenport and Muncey have recorded nine possible examples of the disease in the

children of choreic-free parents who did not die young. They directed attention to the fact that a simple Mendelian dominant may occasionally fail to manifest itself, citing as a parallel example the polydactyl condition of poultry, guinea-pigs, and man. Further observations on this point would be helpful.

Discussion

Our cases, while illustrating the essential features of the disease, in addition offer points for further consideration, as they appear to be less widely appreciated in this country. Huntington, in his original papers, recognized the main characteristics of the disease and vividly outlined, in three short paragraphs, the sufferings of his Long Island patients. Later American observers, notably Davenport and Muncey, added to our knowledge of the disease and provided evidence that marked deviations from the typical picture occur. In our investigations we have found examples of some of these atypical forms, which Davenport termed 'biotypes', and we propose now to consider the main aberrations in some detail.

The age of onset. Usually described as beginning between the ages of 30 and 50 years, many cases have now been reported which show that such is by no means always the case. Huntington himself was of the opinion that the disease always started in late adult life. He wrote 'I do not know of a single case that has shown any marked sign of chorea before the age of 30 or 40 years, while those who pass the fortieth year without symptoms of the disease are seldom attacked'. In Davenport and Muncey's series, however, there were two cases in which the chorea commenced soon after birth, while one-sixth commenced before the twentieth year, and one-fourth before the thirtieth year. Stephens (1892) reported a case which began in infancy, although there was some doubt concerning the true nature of the case, while Gray (1892) and Sinkler (1886) have both described true congenital cases. Owensby's (1925) first case occurred in a twin of choreic ancestry at the age of 4 years, dying in her ninth year in the terminal stages of the malady. Two years later her brother, aged 11 years, became choreic and in 1934 was 'in a pitiable state of dementia and chorea, bedridden—end approaching'. Jolly (1891) saw a case in which chorea and epilepsy began at the age of 9 years, while Osler (1894) studied a case at the Johns Hopkins Hospital beginning in the eighteenth year. Cases showing the onset in the second decade have also been described by Hoffmann (1888), Peretti (1885), and Suckling (1900), while Mackey (1904) has reported two or three cases commencing in the third decade. In England, Critchley, reviewing the cases seen at the National Hospital, Queen Square, found one aged 20 years.

An analysis of our cases in which the age of onset is known is given below in tabulated form (Table I), from which it will be seen that the majority conform to the usual description. Two however, Cases 9 and 10, showed their first signs of chorea at the age of 14 years and 20 years respectively. The onset in Case 2 was in the sixty-first year.

In a tainted family group studied by Worster-Drought and Allen (1929), two sisters, aged ten and eleven years respectively, developed twitching and choreic movements. Movements persisted in the younger girl until her death in childbirth at the age of 25 years, while her sister was still affected at the age of 30 years. As the father, who came of choreic stock, showed no signs of the disease, and because it was not possible to examine the girls, the authors considered a diagnosis of Huntington's chorea very unlikely and one of conversion hysteria more probable. The authors did not mention

TABLE I

Showing the Age at Onset of 21 Cases of Huntington's Chorea

<i>Age at onset.</i>	<i>Case No.</i>	<i>Age at onset.</i>	<i>Case No.</i>
14 years	9	45 years	20 and 21
20 "	10	46 "	3
28 "	19	49 "	15
30 "	14	50 "	12, 13, and 18
31 "	16	53 "	17
38 "	2 and 4	55 "	5
40 "	1, 6, and 8	61 "	11
42 "	7		

the father's age, so one cannot say whether he had died before the usual age of incidence. A critical study of our two cases leaves no doubt in our minds that they are true examples of Huntington's chorea. As Jelliffe has remarked, 'there is a greater likelihood that so-called hysterical movements will turn out to be choreas than the reverse, especially in younger children'.

The law of anticipation. Some observers have attempted to show that the age of onset tends to recur earlier in each generation than in the preceding, but Davenport and others have concluded that there is no good evidence of this. On the whole, our material seems to support the latter conclusion. But in family B of our series the age of onset in the second, third, and fourth generations was 61, 42 and 40, and 14 and 20 years respectively. These five cases are all alive—a unique occurrence—and have been personally studied by us so that accurate dates are available. The apparent anticipation is broken, however, in the first generation when the disease began in the fiftieth year.

Mental degeneration preceding the chorea. Impressed by the frequency with which they met dementia without chorea in the children of choreic parents, and by the occasional tendency for the dementia to precede the chorea, Davenport and Muncey suggested the hypothesis that the dementing factor in a choreic strain may be inherited independently of the other symptoms. This agrees with their other observation, discussed later in this paper, that in tainted families an unduly high incidence of neuropathic conditions is frequently encountered. In England, Curran (1930) has reported an example of this type, a married woman of choreic stock who became demented in her thirty-fifth year and developed a slurring dysarthria and a clumsy gait. In our series, Cases 1 and 2, brothers, and of a family showing the complete

form of the disease in other members, were demented for ten years and eight years respectively before choreiform movements developed. Such cases, frequently presenting a picture similar to that of general paralysis, may cause great difficulty in diagnosis if the hereditary nature of the disease is not disclosed.

Chorea without mental degeneration. We have not observed personally any cases of this nature, but the mother of Cases 20 and 21, although choreic for fifteen years, was said to have suffered no apparent disorder and died suddenly of heart failure in her sixtieth year.

The progressive element absent from the disease. All our cases have been progressive in nature, although the rate of progress has been variable. Some have been rapid such as Case 16, who developed the disease at 31 and was certified and bedridden at 35 years of age; others, such as Case 19, who was choreic for eleven years, progressed but little for many years before becoming finally incapacitated. In the early stages of the disease the movements can, to some extent, be controlled and sometimes stop for a short period to return when the patient becomes agitated and worried.

The pre-choreic personality. The knowledge that some types of insanity tend to recur more frequently in one type of person than in another led investigators to study personality traits in potential choreics. Just as the 'schizoid' type of individual might develop schizophrenia, and the 'pyknic' type manic-depressive psychosis, so in Huntington's chorea it was thought there might be some type of temperament which would indicate those members of a generation prone to develop chorea in adult life. The identification of such potential choreics would appreciably aid early diagnosis and enable marriage and reproduction to be discouraged. As it is, the majority of patients marry and acquire progeny before the chorea appears and so a new generation of patients is already in existence.

Davenport and Muncey have concluded that there is no universal premonitory symptom and that it is impossible to foretell which children of a generation will develop chorea. Many of their patients had been cheerful, bright, unselfish, and considerate, but others, the majority, were irritable, nervous, or excitable. Hughes found that 32 per cent. of her cases betrayed no abnormality before the onset of the disease, while the remainder showed signs of instability, stubbornness, seclusiveness, &c. She agreed with Davenport and Muncey, however, that one could not usually identify the future choreic patient. Of our 24 cases information concerning the pre-choreic personality was available in 19 and this is analysed in Table II.

Nine, approximately 50 per cent., were of an agreeable nature, two showed signs of emotional instability, while two were shy and unsociable. But when these personality types were compared with the family temperament as a whole, a close correspondence was apparent as shown in Table II. From these observations we conclude that, as the pre-choreic temperament is closely similar to that of the family as a whole, it is impossible to define any true premonitory traits such as might identify potential choreic

individuals. The marked change in personality that frequently occurs early in the disease, to which we have already made reference, only serves to corroborate these findings.

Association with epilepsy. Huntington's chorea is occasionally complicated by fits and these may precede the onset of chorea, develop simultaneously with it, or appear during the course of the disease. Notkin (1931), reviewing the literature on this subject, found that of 21 reported cases, in ten instances the convulsive attack preceded the onset of chorea, while in seven they appeared during the course of the disease, and in four others they became

TABLE II

The Pre-choreic Personality in 19 Cases of Huntington's Chorea and a Comparison with the Family Temperaments as a Whole

<i>Family.</i>	<i>Case No.</i>	<i>Personality.</i>	<i>Average family temperament.</i>
A	1	Agreeable	Agreeable but moody. Observations on 36 individuals
"	2	Agreeable	
"	3	Agreeable	
"	4	Agreeable	
"	5	Stubborn	
"	6	Agreeable	
B	7	Placid, reticent	Great variation, extending from shyness and reserve to loquacity and adaptability. Observations on 36 individuals
"	8	Shy and unsociable	
"	9	Agreeable	
"	10	Placid	
"	11	Agreeable	
"	12	?	Nervous and unreliable. Observations on 30 individuals
C	13	Emotionally unstable	
"	14	Emotionally unstable	
"	15	Aggressive and moody	Agreeable and placid. Observations on 16 individuals
D	16	Agreeable	
"	17	Agreeable	
"	18	Aggressive	Nervous and reserved. Observations on 29 individuals
E	19	Shy and unsociable	
"	20	Moody	
"	21	?	
"	22	?	?
F	23	?	
"	24	?	

manifest at about the same time as the chorea. None of our personally observed cases developed epilepsy but Case 18, an aunt of Case 16, experienced frequent 'fits' from the age of 51 years, a year or so after she developed chorea. They recurred at intervals of three or four weeks until her death at the age of 61 years, and, as far as can be judged, seem to have been typically epileptic in character. Consciousness was usually lost, she frothed at the mouth, and 'kicked about on the floor'. She did not become demented, was not certified, and died at home. None of her family or relatives suffered from epilepsy, and, except for the choreic individuals, they are free from any nervous complaint.

The occurrence of epilepsy in non-choreic members of affected families has also been witnessed. Davenport and Muncey found among 3,000 relatives

of 962 choreics, 39 instances of epilepsy and 19 instances of spasms in infancy. Entres (1921) recorded convulsive attacks in nine instances and Ladame (1900), Schlesinger (1892), Geve (1913), and Muller (1903) have described similar findings. In our own investigation, however, we found only one epileptic, a girl of 19 years, among 152 relatives. The daughter of a choreic father, namely Case 19, she suffered from the age of 7 years from typical grand-mal attacks four or five times every month. It is doubtful whether the association is anything more than mere coincidence, although Notkin considers there is some relationship between Huntington's chorea and the idiopathic epilepsies. Many chronic brain diseases, whether of an inflammatory or degenerative nature, may be attended by convulsions. Collier wrote 'Injury to the brain of any nature whatever, whether from violence without or from disease within, may cause epilepsy'. In several of the recorded cases of epilepsy complicating Huntington's chorea in which autopsy findings have been available, other pathological conditions have been observed which in themselves may have been responsible for the epileptic attacks. Notkin emphasized that a condition of pachymeningitis was found in both Kurella's (1887) and Dost's (1915) cases, while in one of Hoffmann's (1888) cases syringomyelia was also present. Goldstein's (1897) patient was an alcohol addict (although it must be remembered that the choreic patient is frequently a chronic alcoholic), no convulsions occurred during his attacks of unconsciousness and, as he died of coronary thrombosis, the attacks may have been syncopal in nature. A history of head injury was obtained in each of the cases of Dost and Althous (1880) and in one of Hoffmann's, while Dunlap's (1927) patient sustained a 'fall' a week before death, during which time she had several convulsions. The few remaining cases are thus so infrequent as to lend no support to the view that there is any association between epilepsy and Huntington's chorea.

Infant mortality rate in affected families. More common than epilepsy in the families of our series has been death in the early months of life, as may be seen on reference to the charts. Twenty-five of 219 individuals died during the first six months of life, and for several of these there was a history of 'spasms', or 'fits'. In Family B alone there were 19 such instances. Wassermann tests of several members of the families concerned did not suggest a luetic origin of these premature deaths. Abiotrophy may well be the explanation here, signifying as it does some developmental defect. Kehrer (1928), in Germany, has also noticed this high infant death-rate in families of Huntington's chorea.

Non-choreic members of tainted families. A study of the non-choreic members of affected families is an important one, not only because they may include a certain number of future choreics but also because they may exhibit other nervous diseases signifying a general neuropathic inheritance of which Huntington's chorea is but one manifestation. The existence of atypical forms of the disease and the apparent divorce of the mental and choreic factors known to occur, would seem to suggest this, so that an

investigation of unaffected relatives becomes instructive and of some importance.

Huntington wrote 'In all the families, or nearly all in which the choreic taint exists, the nervous temperament greatly preponderates, and in my grandfather's and father's experience, which covered a period of seventy-eight years, nervous excitement in a marked degree almost invariably attends upon every disease these people may suffer from, although they may not in health be over-nervous'. Davenport and Muncey, in their extensive field investigation, found in 3,000 relatives of 962 choreics, 39 instances of epilepsy, 19 of infantile convulsions, 4 of encephalitis, 73 of feeble-mindedness, 11 of Sydenham's chorea, 47 of meningitis, 41 of hydrocephalus, and 9 of tics, concluding that there was thus sufficient statistical evidence to warrant the belief that the disease develops in certain strains characterized by general nervousness and liability to a great variety of nervous diseases. Hoffmann (1888), Lepilli (1888), Diller (1890), Greppin (1890), Jolly (1891), Remak (1891), Ladame (1900), and Frank (1904) were all of the opinion that some relationship exists between Huntington's chorea, epilepsy, and other nervous disorders. Hamilton (1908), however, in a study of the relatives of 27 cases of Huntington's chorea, concluded that 'ordinary nervous and mental diseases are conspicuous by their absence'. Rosanoff (1923), concluding a similar study, stated that 'other nervous and mental diseases occurred relatively so infrequently as to be readily accounted for as coincidences essentially without relation to the chorea itself'. Hughes (1924), reporting the results of a wide investigation, said 'at first glance the occurrence of nervous traits in these families seems to be more than incidental, but the actual percentage is very small, and, in the absence of comparative data, Rosanoff's conclusions seem to be borne out'.

In our investigation of 152 non-choreic relatives no example of mental or nervous abnormality occurred except in three individuals. One girl, mentioned above, was an epileptic, while the remaining two, a brother and sister respectively of Case 19, showed signs of mental abnormality which, however, might be interpreted as early signs of the disease itself. Generally speaking, these individuals appeared to be ordinary examples of the working class in which they were found. The majority were intelligent, industrious, and sober folk whose sole cause of agitation was the presence of the disorder in their midst. We cannot, therefore, subscribe to the findings of Davenport and Muncey that choreic families as a whole carry with them numerous manifestations of their neuropathic inheritance. Nor can we conclude with Hattie (1909) that alcoholic addiction characterizes so many members that lay folk considered the disease to be a result of that habit. Lastly, our study of these families leaves no doubt in our minds that they differ in no essential way from other families of the same class, and that the general shiftlessness and inefficiency found by See (1923) in his families cannot be corroborated. The consensus of opinion, then, appears to be that tainted families do not include a greater percentage of ineffectuals and nervously

afflicted than can be reckoned normal. It may be, however, that in certain American states, where the disease is certainly commoner and where intermarriage has resulted in very complex strains, abnormalities are more frequent.

Social significance. No observer who has studied a group of these patients can fail to be pained by the distress of a family when this disease appears in one of its members. The patient is usually married, as were 16 of our 24 cases, and has children; the disease attacks at the prime of life usually, leaves no peace to the victim, and, after an illness lasting ten or fifteen years, reduces him to a demented and helpless condition which is only terminated by death. The sufferings of the patient are reflected in the minds of his relatives, who watch in fear and despair, knowing that they too may share a similar fate. Anxiety neuroses and suicides have been reported by several observers, but in the patient himself lack of insight seems often to prevent this. Yet there is no effort to avoid marriage or reproduction, indeed these families are prolific and tend rather to hide the evidence of their tainted blood. Friction and unhappiness await the individual who marries unknowingly into such stock. To the authors there appears to be no other mental disease which so relentlessly adheres to its laws of inheritance. Parents afflicted with other forms of nervous disorder do not as a rule transmit special diseases, but only a tendency to neuropathy as a whole, which may not develop into distinct diseases without certain environmental disturbances. Not so in Huntington's chorea, where each generation is affected, where a simple Mendelian dominant transmission is demonstrated, so that every patient heterozygous for the disease may expect an average of 50 per cent. of affected offspring. In our series there are at least 100 individuals now living of whom 50 per cent. are liable to develop the disease.

For these reasons then—the incurable nature of the illness, the direct mode of hereditary transmission, and the incidental tragedies in its wake—we strongly recommend the adoption of some form of control. Voluntary restraint we hardly think likely to be effective in our class of patient at least, although several of them, having witnessed the disease, have realized that marriage should be discouraged. Perhaps, with repeated advice and education, some would voluntarily abstain from marriage, but the majority would no doubt be prepared to accept the even chance that nature offers them. We are thus left with the conclusion that only legislative measures will eventually succeed in eradicating the disease.

Original source of our cases. Four of the six family groups studied originally came, four and five generations ago, from the county of Pembroke. Three of these moreover, came from the south of that county, from the neighbourhood of Haverfordwest and Milfordhaven; so that, in that district, in a more or less detached rural community, there may well be hidden away more similar cases. It may be interesting to mention here that it is common lay knowledge in South Wales that in those rural parts intermarriage is frequent and practitioners have informed us that mental abnormalities seem

to be more frequent there. We are not suggesting, however, that such apparent neuropathy is a consequence of this intimate mixture of stock, or that it is in any way related to the conditions we have described.

Summary

1. A study of 24 cases of Huntington's chorea, 15 of which were personally examined and observed by us for a year or more, is presented.
2. The existence of atypical forms of the disease is discussed and illustrative examples furnished.
3. An investigation of unaffected members of tainted families failed to reveal any sign whereby the future choreic could be identified. Unaffected members were healthy, normal, and free from other nervous complaints.
4. A high infant death-rate was recorded in some of the families studied.
5. The social significance of the disease is considered and prevention of marriage of any member of an affected family is advocated.

We wish to express our indebtedness to Professor A. M. Kennedy for his advice and criticism during the course of this investigation, to Dr. J. R. Payne, Medical Superintendent of the Ely Homes, Cardiff, to Dr. D. R. Owen, Medical Superintendent of the Glamorgan County Mental Hospital, Bridgend, and to Dr. N. Moulson, Medical Superintendent of Swansea Mental Hospital, for their permission to investigate cases under their care.

Case Histories

Family A. Cases 1, 2, 3, 4, 5, and 6

Case 1, History. This patient came under observation in 1932 at the age of 55 years. By occupation a tinworker, he had, until the age of 40 years, been a steady man, conscientious and agreeable. From that age, however, in his wife's words 'he became gradually a changed man'; bouts of anger were common and disturbed the household. He became violent towards his wife and children, destructive impulses frightened them, and he took to alcohol in a remarkably vicious manner. For two or three years his work did not apparently suffer, but gradually there developed an incurable obstinacy and laziness. He would fail to get up in the morning and frequently refused to do his particular job. This eventually resulted in his dismissal, and from that day, aged 43 years, until his death 17 years later, he did no more work. Until he reached his fiftieth year no choreiform movements appeared, but meanwhile his mental and moral disintegration had steadily progressed, so that he became a suspicious, hallucinated dement. He thought his neighbours and the police were intent on killing him, he would walk naked about the house at night and disappear for days on end. During this time he had little or no insight into his condition, memory and judgement were poor and threats of suicide frequent. Involuntary movements and speech defects appeared about the same time at the age of 50. His gait became unsteady and his speech thick, so that in the street he was accused of drunkenness. The movements gradually involved the head, trunk, and limbs and never ceased

except during sleep. At the age of 55 years he was admitted to a mental hospital on certificate.

Examination. His facial expression was dull and his attitude apathetic. He looked pale and ill, and when questioned replied in a thick voice with abrupt phrases. He was in a perpetual state of restlessness, eyes, lips, head, trunk, and limbs all participating to produce a picture of incessant motion. Walking was grotesque—arms and legs shooting out in abnormal directions—but the movements lessened somewhat when he sat down. Memory, both for recent and remote events, was poor. Intelligence was very limited, and he was depressed and suspicious. He seemed to have no insight and his flow of thought and speech was disconnected and irrelevant. Orientation was poor but he appeared to suffer no delusions or hallucinations at the time.

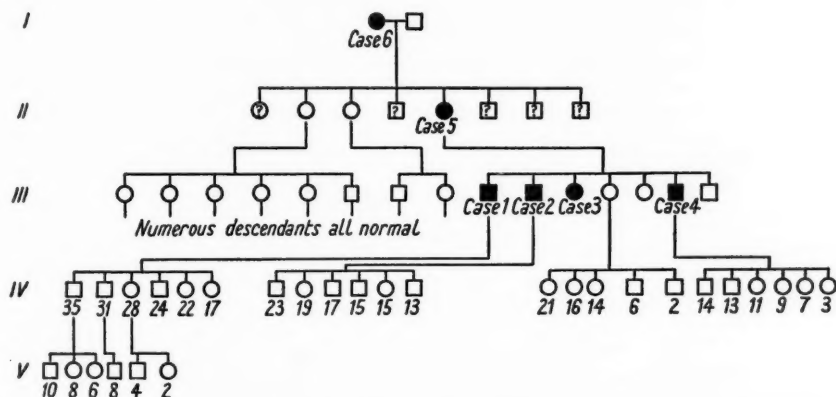


Chart I. Pedigree of Family A. Affected persons indicated by black symbols. □ = Males. ○ = Females. Numbers beneath symbols in fourth and fifth generations indicate present age in years.

Cranial nerves were all normal. Motor power of the limbs was fair and the tone normal; tendon jerks in arms and legs were exaggerated, the plantar and abdominal reflexes were normal, and there was no clonus. As far as could be judged sensation was normal and co-ordination, in spite of the spontaneous movements, was good. Cardiovascular, respiratory, and alimentary systems were normal. Blood-pressure was 138 systolic and 80 diastolic. The Wassermann reaction of the blood was positive, but negative in the cerebrospinal fluid. Examination of the latter showed one cell per c.mm., protein 25 mg. per 100 c.c., chlorides 720, sugar 45, and Lange's colloidal gold curve 0000000000.

During his stay in hospital he became gradually more demented and died, bedridden, at the age of 60 years.

Case 2, male, aged 59 years, brother of the above patient. Mental degeneration commenced at 38 years, and chorea at 46 years. Abusive, violent, and depraved. Speech indistinct, and memory, orientation, and insight entirely lacking. Cranial nerves normal. No loss of power; reflexes normal. W.R. of blood and C.S.F. negative. C.S.F. clear, cells 3, protein 37 mg. per 100 c.c., sugar 37, chlorides 670, and Lange's curve 0000000000.

Case 3, female, aged 48 years, sister of the above patients. Two years ago showed signs of early chorea; became fidgety, restless, and prone to attacks

of depression and silence. No delusions or hallucinations. She would not venture out of doors because she said people watched her twitching. Examination revealed no other abnormality of the nervous system. Heart, lungs, and abdomen normal. W.R. tests of the blood and C.S.F. were negative. C.S.F. showed cells 3 per c.mm., protein 34 mg. per 100 c.c., sugar 40, chlorides 700. Lange 0000000000.

Case 4, male, aged 38 years when choreic movements appeared. They were attributed to war service at the time and he died suddenly at 40 years of age of 'heart trouble'. No history of mental troubles.

Case 5, female, mother of the above patients. Developed chorea at 55 years of age, which persisted till her death at 60 years. No mental degeneration occurred, and till the time of her death she was not incapacitated.

Case 6, female, maternal grandmother of cases 1, 2, 3, and 4. She became choreic at the age of 40 years and died, without any mental changes appearing, at the age of 42 years of 'heart failure'.

Family history. Reference to Chart I will show that the above cases were distributed throughout three generations, but unfortunately no trace of the majority of those of the first and second generations could be obtained. In the third generation there are two sisters and one brother who show no sign of the disease. Their children are normal.

Cases 1, 2, and 4 each had six children, all normal. Case 1 has six grandchildren who are similarly free of any abnormality.

Family B. Cases 7, 8, 9, 10, 11, and 12

Case 7, male, aged 50 years, was first seen on admission to mental hospital under certificate. Healthy until 42 years of age, when, after an emotional upset, he became fidgety and restless. Talked incessantly and became very agitated at times. Choreic movements interfered with his work, and at the age of 45 years he was discharged unfit. In his forty-seventh year he developed persecutory ideas; gait became 'drunken' in character and speech indistinct. No hallucinations or violent outbursts.

Examination. Pale, poorly nourished, restless, and confused. Marked chorea; slurring dysarthria and clumsy gait. Gross dementia. Physical examination revealed no untoward sign. W.R. of blood negative. C.S.F. not examined.

Case 8, male, aged 47 years, brother of the above patient. Healthy and normal until the age of 40 years, when, during a time of unemployment he became quarrelsome and untidy in his habits. Commenced to wander the streets at night and was eventually placed in an institution. Chorea commenced while there and has grown steadily worse. Irritable and difficult, prone to violence. Bedridden for the last two years.

Examination. Agitated and restless. Generalized choreiform movements. Speech thick and jerky; unable to walk unassisted. Clearly orientated but insight totally lacking. Gross delusions of persecution. No hallucinations. Apt to become tearful and depressed. Trombone-like tremor of the tongue. Moderate arteriosclerosis. No other physical abnormality. W.R. of blood and C.S.F. negative. C.S.F. gave cells 3 per c.mm., protein 20 mg. per 100 c.c. Lange 0000000000.

Case 9, female, aged 22 years, niece of the former patients Cases 7 and 8. Her father was killed in an accident at the age of 25 years and was healthy and normal. In view of the facts that two of his brothers, and two of his three children are afflicted, it is probable that he too would have become

choreic in later life. His eldest child, the present patient, was normal in every way until the age of 14 years, when she was observed to be clumsy at times so that she dropped things frequently. No definite choreic movements appeared, however, until her nineteenth year. Since that time she had grown steadily worse and severely ataxic, choreic and childish. She experienced no emotional upsets and had suffered no delusions, hallucinations, or epileptic attacks. She had had no other illness, but of late years had lost considerable weight and was somewhat wasted.

Examination. Extremely restless and choreic, the movements chiefly affecting the face and left side of the body. They were bizarre, abrupt and of wide range, accompanied by smacking sounds from her lips. She was childish and of a happy frame of mind, obedient and easily pleased. Memory was good, she was well orientated and suffered no delusions or hallucinations. Speech was thick and jerky, difficult of comprehension. Physical examination revealed no other abnormality. W.R. of blood and C.S.F. negative. Examination of the latter fluid showed cells 1 per c.mm., protein 30 mg. per 100 c.c. Lange 0000000000.

Case 10, male, aged 25 years, brother of Case 9, presented early signs of the disease. His parents realized this and suggested that we should examine him. At school he had made slow progress and on leaving was unable to obtain employment. When twenty years of age his parents noticed that he showed signs of his sister's illness, as he continually fidgeted and became awkward about the house. Involuntary movements first appeared in the legs and later spread to involve the shoulders and arms. Speech had remained unaffected, and apart from the retention of certain childish habits he presented no gross signs of mental change. His only other illness was measles and he had had no epileptic attacks.

Examination. Blank childish expression. When first seen he sat mute in a corner and did not attempt to reply to any of our questions. His hands made short, jerky movements of flexion and extension, his fists opening and closing abruptly, while his head turned quickly first one way and then another. The facial muscles were not involved except for frequent loud sniffing movements which were evidently a source of constant worry to his parents. On one occasion when we were present, jerky movements of his legs and body, although not of great amplitude, succeeded in moving the stool on which he sat half-way across the room in a few minutes. Speech was slow but clear and his gait was unaffected. Memory, insight, and orientation were good. Physical examination showed no other sign of disease. W.R. of the blood was negative. C.S.F. was not examined.

Case 11, male, aged 65 years, maternal uncle of Cases 7 and 8. Developed chorea at the age of 61 years, a year after retiring on pension from his job as a colliery engine-driver. Attributed his illness to a fright at work. Severely choreic; speech practically unintelligible; memory, insight, orientation grossly affected. Spent most of his time sitting by the fireside, muttering away to himself. Moderate arteriosclerosis. No other physical abnormality. W.R. of blood and C.S.F. negative. C.S.F. examination showed cells 4 per c.mm., protein 40 mg. per 100 c.c. Lange 0000000000.

Case 12, female, mother of Case 11, Chorea appeared at the age of 50 years and mental degeneration soon followed. Certified at 57 years of age and died in a mental hospital at the age of 61 years. She was severely choreic and demented.

Family history. The distribution of the disease through four generations is illustrated in Chart II. The mother of Cases 7 and 8 died in childbirth

at the age of 35 years and was healthy and normal. However, as her mother, brother, and two of her four children acquired the disease it is probable that she was a potential choreic. Only four of her children survived infancy, nine dying during the first six months of life of 'wasting', 'spasms' or 'fits', or causes unknown. No evidence of syphilis. Her eldest child, a woman of 45 years, had had 13 children, five of whom died in infancy of similar obscure conditions. The remainder were all normal.

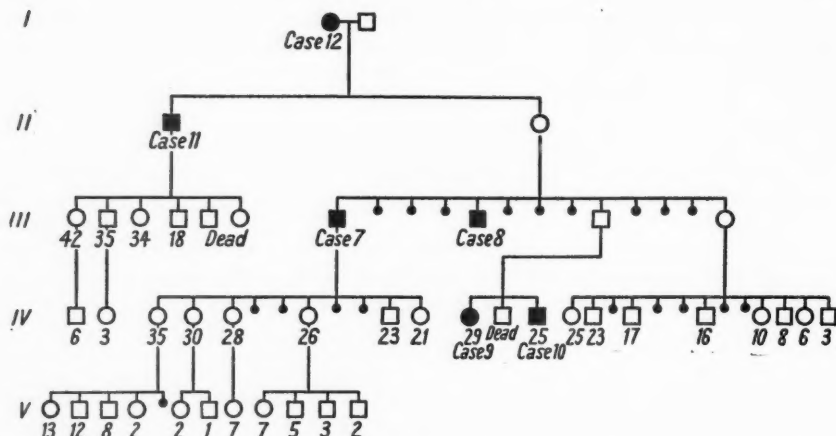


Chart II. Pedigree of Family B. Affected persons indicated by large black symbols. □ = Males. ○ = Females. Small black circles indicate persons dying in the first six months of life. Numbers beneath symbols in third, fourth, and fifth generations indicate present age in years.

Case 7 had 10 children, four of whom died in infancy. The remaining six and their children are normal.

Case 8 had no children.

Case 11 had had six children; two died of diphtheria, while the surviving four are healthy.

Thus, in this family group there are 19 instances of death in infancy of obscure causes.

Family C. Cases 13, 14, and 15

Case 13, female, aged 61 years, unmarried. Developed chorea at the age of 50 years. Attributed to a fall in which she struck her head, a few weeks before the appearance of chorea. It had progressed steadily and the patient had been an inmate of various institutions for ten years. She was bed-ridden, severely choreic and demented. The choreic movements persisted at times during light sleep and she required constant attention because the movements at times almost threw her from her bed. No delusions or hallucinations. Physical examination showed no evidence of disease of the cardiovascular, respiratory, or alimentary systems. W.R. of blood negative. C.S.F. not examined.

Case 14, female, aged 56 years, sister of Case 13. Was 'peculiar' at the age of 30 years, prone to emotional upsets and strange behaviour. Chorea developed at 45 years of age by which time she was quite unstable and hallucinated. Attempted to murder her husband on one occasion. Speech

became affected at 50 years of age. Violent, depressed, and now bedridden and helpless. Severe arteriosclerosis. No other physical abnormality. W.R. of blood and C.S.F. negative. C.S.F. examination showed cells 4, protein 40, and Lange 0000000000.

Case 15, female, mother of Cases 13 and 14, became choreic at the age of 49 years. Quarrelsome, violent, was certified at the age of 60 years and died in a mental hospital at 65 years. Bedridden for the last two years.

Family history. Chart III. Data concerning four generations of the family are available. In the first, the maternal grandfather of Cases 13 and 14,

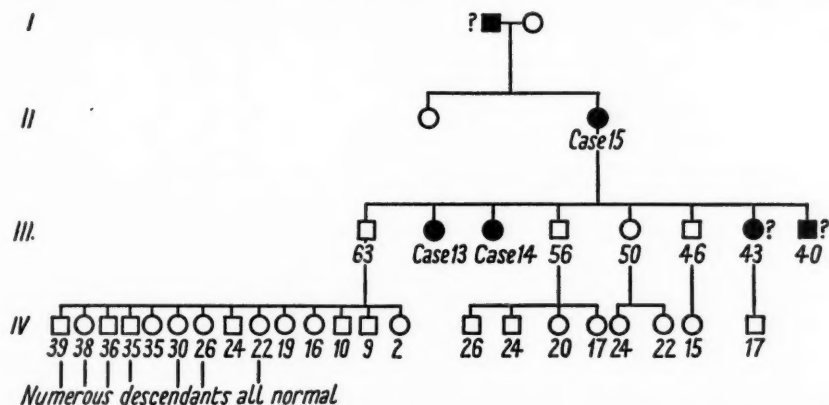


Chart III. Pedigree of Family C. Affected persons indicated by black symbols. □ = Males. ○ = Females. Numbers beneath symbols in third and fourth generations indicate present age in years.

a sailor, was normal and healthy until middle age, when he became unsteady on his legs and was apt to fall down. He fell from a pier and was drowned. As his wife lived to be 75 years of age and showed no sign of the disease, it is probable that he was an early case of the disease and transmitted it to his daughter, Case 15.

In the second generation no trace of the sister of Case 15 was obtained.

There were four unaffected individuals in the third generation and their children were normal and healthy. In addition there were two individuals, the youngest brother and the youngest sister, who presented certain signs of abnormality. The brother was single, aged 40 years, and had repeatedly refused us an interview. He was an engine-driver, and we were told that on two occasions he 'had some fit or attack' while driving a train, with somewhat disastrous results. He was reputed to be 'never still' and was of an unhappy disposition. No other facts about him could be obtained. He was probably another instance of chorea. The youngest sister had also refused an interview. She was 47 years of age, married, and had been an inmate of a private mental home on a few occasions. She, too, was probably a choreic person.

Family D. Cases 16, 17, and 18

Case 16, female, aged 39 years, single, showed first signs of mental change at the age of 31 years. Choreiform movements began at 32 years of age. Speech became thick and jerky, gait unsteady. Acquired a vicious temperament; persistent delusions of persecution rendered her actions violent and

dangerous. In hospital she improved for a time, but she was bedridden and helpless. Severe generalized choreiform movements. She could give no account of herself and memory orientation and insight were markedly affected. Moderate arteriosclerosis. Physical examination showed no other abnormality. W.R. of blood and C.S.F. negative. C.S.F. examination revealed 4 cells per c.mm., protein 26 mg. and Lange 0000000000.

Case 17, male, father of the above patient. Chorea appeared at the age of 53 years and persisted till his death at 63 years. Ataxia, thick voice, and childish during the last few years. He was not certified.

Case 18, female, sister of *Case 17*. Chorea commenced at 50 years of age.

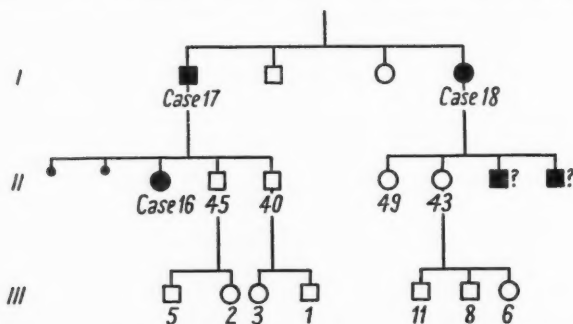


Chart IV. Pedigree of Family D. Affected persons indicated by black symbols. □ = Males. ○ = Females. Small black circles indicate persons dying in the first six months of life. Numbers beneath symbols in second and third generations indicate present age in years.

'Fits' also present, which began a year or so after the chorea and recurred at intervals of a few weeks till her death at 61 years. They were frequently accompanied by loss of consciousness and convulsive phenomena. No gross mental degeneration.

Family history. Chart IV. Three generations were traced. There were two unaffected individuals in the first generation; they were both single. *Case 17* had five children, two of whom died in infancy; the first at six months and the second soon after birth. Two surviving children were normal and had healthy children. *Case 18* had four children, two of whom were alive and healthy. Two younger children, males, died in their third decade of similar illnesses, which the relatives described as 'brain fever'. No details of these illnesses could be elicited, but they lasted several years and were at times accompanied by delirium and excitement. It is possible that they too suffered from the family ailment.

Family E. Cases 19, 20, 21, and 22

Case 19, male, aged 40 years, married. Choreiform movements commenced at the age of 28 years. Speech affected in his 35th year. At 39 he showed signs of mental degeneration which rapidly increased and rendered him certifiable a year later at the age of 40 years. W.R. of blood negative. C.S.F. not examined. No abnormality of heart, lungs, or abdomen. Died of pneumonia while in mental hospital.

Case 20, male, father of *Case 19*, became choreic at the age of 45 years. Admitted to an institution at 55 years of age. Died at 59 years of age, severely choreic and demented. Uncertified.

Case 21, male, brother of *Case 20*, developed chorea at 45 years. Then showed no sign of mental change. Has since been lost sight of, although a few years ago he was reported to be in much the same condition except that his speech was difficult to follow at times.

Case 22, female, mother of *Cases 20* and *21*. Chorea was present for 15 years or so before her death at the age of 60 years. No apparent mental degeneration. Died suddenly of heart failure.

Family history. *Chart V*. There were five unaffected children in the third generation, all of whom have normal and healthy children. The third child, now a married woman of 41 years, had two children who died in infancy.

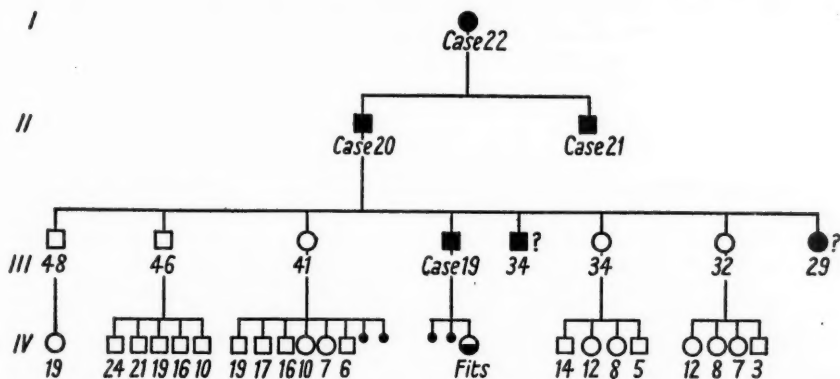


Chart V. Pedigree of Family E. Affected persons indicated by black symbols. □ = Males. ○ = Females. Small black circles indicate persons dying in the first six months of life. Numbers beneath symbols in third and fourth generations indicate present age in years.

Case 19, the fourth child, had three children, two of whom died in infancy. The third, a girl of 19 years, was a confirmed epileptic. One attack was witnessed and was a typical grand-mal attack. They commenced at the age of 7 years. She was normal in every other way.

The fifth child, a man of 34 years, single, was seen on one occasion, and although he presented no signs of chorea was obviously demented. He refused to speak to us and showed no sign of understanding the object of our visit.

The youngest child, a married woman of 29 years, was nervous and restless. There was no chorea present, but she was tearful and depressed, and said she was developing the family illness. She had threatened to commit suicide on several occasions. Possibly she is an early case of the disease or else one of an anxiety neurosis.

Family F. Cases 23 and 24

Case 23, male, aged 67 years, first seen in 1937 on admission to mental hospital under certificate. Retired on pension at 58 years of age and had been choreic for at least eight years. He was grossly demented, and could give no account of himself. He had delusions of grandeur. Moderate degree of arteriosclerosis. W.R. of blood and C.S.F. negative. C.S.F. examination showed cells 2 per c.mm., protein 15 mg. per 100 c.c., sugar 81, chlorides 780. Lange 0000000000. Pandy negative.

Case 24, female, aged 64 years, sister of *Case 23*. Had been an inmate of

an institution for five years. Nothing known of her previous to that time. Typical choreic movements and gross dementia; very depraved. She was bedridden. W.R. of the blood negative. C.S.F. not examined.

Family history. Nothing was known of their family except that their father was alive and mentally abnormal. He was about 87 years of age.

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LUNG CHANGES IN INFLUENZA¹

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and Hammersmith Hospital, L.C.C.)

With Plates 15 to 17

THE demonstration of a filtrable virus pathogenic to ferrets in patients suffering from a disease clinically diagnosed as influenza (Smith, Andrewes and Laidlaw, 1933) and the subsequent demonstration of a similar virus in other outbreaks in various parts of the world (Francis, 1935; Burnet, 1935) have shown that this virus is the probable primary agent in some of the outbreaks of acute respiratory disease with high local infectivity which are called influenza. The further experience of workers with the virus has shown that it can be isolated only from cases occurring during epidemics (Andrewes, Laidlaw and Smith, 1934; Fairbrother and Hoyle, 1937). These observations render it possible to make an etiological diagnosis of 'virus influenza', and to hope thus to define a recognizable clinical picture of this disease from the mass of cases which have been labelled 'influenza' in the past, often without conviction except during pandemic times.

With this object in view, a study was made of cases of influenza admitted to Hammersmith Hospital during the epidemic of December 1936 and January 1937. Provision was made for the admission of such cases as far as possible to two wards which were cleared for the purpose.

The virus was demonstrated in four of these cases by Dr. C. H. Andrewes at the National Institute for Medical Research. Three of these cases were without serious pulmonary involvement, the virus being isolated from throat-washings taken on the second or third day; in the remaining case the virus was isolated from the lung at autopsy. In addition, unsuccessful attempts to demonstrate the virus were made in two instances, once from throat-washings of a pneumonic case on the eighth day, and once from the lung of a patient dying on the ninth day. As isolation of the virus is uncertain after the first four days, and as patients were rarely admitted to hospital before the fourth or fifth day, it is clear that opportunities for obtaining suitable material for virus investigation were rare.

As it was not possible to confine observations to virus-positive cases, partly for the above reasons, and partly because expenditure of ferrets required for the present methods of isolating the virus necessarily limited

¹ Received July 6, 1937.

the number of cases in which tests could be performed, inferential evidence of the diagnosis had to be accepted in most instances.

The typical onset was characterized by relatively sudden prostration, sometimes with shivery sensations, occasionally amounting to a rigor. Headache and aching pains in the lumbar region and limbs were early symptoms. Cough occurred early, often on the first day. Throat symptoms

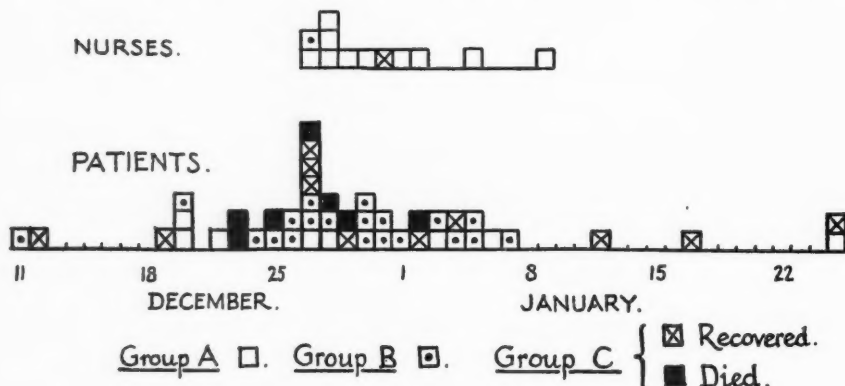


FIG. 1. Date of onset of symptoms.

were not prominent, dryness and discomfort rather than soreness being usual: in some cases complaint of soreness of the throat was first made on the third or fourth day. Eye symptoms—soreness and lachrymation, and less often pain behind the eyes or photophobia—were present at the onset in half the cases. Nasal symptoms were rarely present at the onset; a mild coryza occurred in about half the cases on the second or third day. Anorexia was constant from the onset. Vomiting occurred during the first three days in about one-fifth of the cases.

When a careful history, confirmed and amplified if necessary by a relative of the patient, showed an onset of this type, it was considered that cases could be regarded as primarily of virus influenza, occurring as they did in an outbreak from which the virus had been isolated. Further points supporting this assumption are that the epidemic was widespread at this time, and that the virus was being isolated from cases in various localities in England (Hoyle and Fairbrother, 1937; Stuart-Harris, 1937); and that cases with a history of onset of the above type were confined to the epidemic time.

Fifty-eight cases regarded as influenzal in origin were observed in the latter half of December 1936 and in January 1937. Inevitably, some cases of influenzal origin were admitted to other wards of the hospital, but only those personally observed and recorded are included in the present series. It was soon found that, as was to be expected, most cases admitted had evidence of pulmonary involvement; less severe cases usually being treated at home. Attention was therefore directed principally to a study of the

lung changes. The series includes a small outbreak among the nursing staff of the hospital, composed of 12 cases in all. These included two of the cases in which the virus was isolated from throat-washings. The date of onset of influenzal symptoms in the patients admitted to hospital and in the cases among the nurses is shown in Fig. 1.

Classification of Cases

The chief difficulty in describing the lung changes observed is that of classifying the various clinical pictures. The types of lesion merge imperceptibly into each other, and any classification must be arbitrary; especially as neither the lung signs nor the radiological evidence of lung involvement bore a constant relation to the duration or severity of the illness. The basis of classification here adopted is the evidence of lung involvement, including physical signs and radiological changes. The presence of consolidation was often very difficult to decide clinically, and in doubtful cases radiological evidence of it was accepted as the most reliable during life. The cases are divided into:—

A. Cases without clinical signs of lung involvement—18.

B. Cases with physical signs of lung involvement but without evidence of consolidation—21.

C. Cases with evidence of pulmonary consolidation—19.

The average age of the patients, excluding the nurses, was 40 years; there was no significant difference between the average ages in the various groups.

A. Cases without Clinical Signs of Lung Involvement

As this paper deals with the lung changes, it is not proposed to discuss in detail the clinical picture of this group. Reference will be made only to those symptoms which may be indicative of affections of the lower respiratory tract.

Of the 18 cases in the group, 10 were members of the nursing staff. In all cases, cough was an early symptom, usually appearing on the first day, sometimes on the second, rarely deferred until the third. It was frequently accompanied by a painful sensation behind the sternum, varying from slight soreness to a severe 'tearing' pain. There was usually no sputum at first; later, in most cases, scanty mucopurulent sputum was produced, though occasionally the cough remained dry: sometimes expectoration was deferred until after defervescence. Cough often persisted for a week or ten days after defervescence. Pyrexia usually lasted only one to three days; in two cases it lasted as long as five days.

Three patients were elderly chronic bronchitic subjects. In these cases an exacerbation of the signs of bronchitis occurred without any unusual features. As the signs in the lungs could not be attributed to the influenza, they are included in this group.

Bacteriological and haematological findings in the cases of this group in which they are available are given in Table I.²

B. Cases with Lung Signs, but without Consolidation

There were 21 cases in this group (see Table III), which includes most diverse forms, varying from some symptomatically indistinguishable from

TABLE I

Group.	Age.	Sex.	Duration of fever.	Leucocytes.				Predominant organisms in sputum culture.	Group.
				Initial.	Day.	Maximum.	Day.		
A	32	F	2	7,000	1	—	—	<i>Strep. haemolyticus, Strep. viridans</i>	B1
	21	F	4	5,000	3	—	—	<i>Strep. non-haem., Strep. viridans, Staph. aureus</i>	
	36	F	2	4,000	2	—	—	<i>H. influenzae, Strep. viridans</i>	
	22	F	3	—	—	—	—	<i>Strep. haemolyticus, Strep. viridans</i>	
	19	F	5	4,500	3	8,000	7	<i>Strep. viridans, Gram-neg cocci, H. influenzae</i>	
	21	M	2	13,000	2	20,000	15		
	39	F	2	4,000	4				
	18	F	2	7,000	2				
	32	F	2	6,000	2	8,000	10		
	30	F	6	7,000	6	11,000	10		
	19	M	4	8,900	5	16,500	10		
	59	F	?	10,000	3	13,500	12		
	63	M	5	8,000	9	15,000	12	<i>H. influenzae</i>	
	53	M	10	—	—	—	—	<i>Strep. viridans, N. catarrhalis</i>	
	47	M	7	—	—	—	—	<i>Strep. viridans, H. influenzae</i>	

* Chronic bronchitic subjects.

those included in group A, to some whose aspect resembled that of a case of severe pneumonia. For descriptive purposes, the group can be divided into two sub-groups, according to the severity of the illness.

1. Fifteen of the cases fall into the 'less severely ill' sub-group.

Of these, five were indistinguishable from those of Group A in symptoms, clinical course and duration, apart from the transient appearance of abnormal lung signs. In two of them, an area at one base showed weak breath-sounds for a period of two days, and then returned to normal. In the other three, fine râles usually only during deep inspiration, or occasional soft medium-pitched rhonchi were heard at the bases or in the axillae on one or two examinations, but there were no alterations in the breath-sounds or percussion-note. One other patient had transient lung signs of this sort, but had a prolonged pyrexia with persistent vomiting, the pyrexia probably not being attributable to a lung condition.

² In Tables I, II, and III, only the predominant organisms in the sputum-cultures are listed. The analysis of the bacteriology of the sputa, below, is based upon a more complete enumeration of the bacterial types present in the cultures.

Nine cases had more prolonged abnormal physical signs of similar type, with pyrexia for a week or eight days, but never became seriously ill. The symptoms consisted of a continuation of the cough, with some dyspnoea and prostration. Sputum became purulent, usually increased to about 20 c.c. to 30 c.c. daily at the end of a week or ten days, and then gradually diminished in amount. These patients usually complained of a more severe form of the retrosternal pain on coughing which was sometimes noted in

TABLE II

Group.	Age.	Sex.	Duration of fever.	Leucocytes.				Predominant organisms in sputum culture.
				Initial.	Day.	Maximum.	Day.	
B 1	25	M	6	8,200	7	9,500	11	<i>H. influenzae</i> , <i>Strep. viridans</i>
	28	F	4	3,400	4	—	—	<i>Strep. viridans</i> , <i>Strep. pseudo-haemolyticus</i>
	27	M	3	6,000	3	12,000	11	<i>Strep. viridans</i> , <i>Staphylococcus</i>
	51	M	?	8,000	6	18,000	12	<i>Strep. viridans</i> , <i>Pneumococcus</i> gr. IV
	29	M	4	5,000	3	—	—	
	32	M	12	13,300	11	17,000	17	<i>Strep. viridans</i> , <i>H. influenzae</i>
	38	F	8	5,200	4	8,000	11	<i>H. influenzae</i> , <i>Strep. viridans</i>
	41	F	7	6,600	7	—	—	<i>H. influenzae</i> , <i>Strep. viridans</i>
	31	F	8	7,200	3	12,000	16	<i>Strep. viridans</i> , <i>N. catarrhalis</i> , <i>Staph. aureus</i>
	34	F	6	6,000	3	14,400	11	<i>H. influenzae</i> , <i>Strep. viridans</i> , <i>N. catarrhalis</i>
	22	M	5	8,000	7	—	—	<i>Strep. viridans</i> , <i>N. catarrhalis</i> , <i>H. para-influenzae</i>
	64	M	6	6,000	8	30,000	13	<i>Strep. viridans</i> , micrococci, <i>Pneumococcus</i> type III
	34	M	6	12,000	8	17,000	11	<i>Strep. viridans</i> , <i>N. catarrhalis</i>
	37	F	?	8,000	5	8,200	9	<i>Strep. viridans</i> , Gram.-neg. diplococci
	8	M	6	11,000	7	21,800	16	Gram.-neg. diplococci, <i>Pneumococcus</i> type II
B 2	36	M	19	17,000	15	19,000	18	<i>Strep. viridans</i> , <i>H. influenzae</i> , <i>N. catarrhalis</i>
	71	F	21	10,000	9	—	—	<i>Strep. viridans</i> , <i>H. influenzae</i>
	53	F	18	18,000	9	34,000	11	<i>H. influenzae</i> , <i>Strep. non-haem.</i>
	31	F	13	26,000	9	38,000	11	<i>Strep. viridans</i> , <i>Pneumococcus</i> type III
	31	F	5	9,500	4	13,500	6	<i>N. catarrhalis</i> , <i>Pneumococcus</i> gr. IV
	55	F	5	—	—	—	—	<i>Strep. viridans</i> , micrococci

cases of group A; in two, there was complaint of pain in the side of the chest on coughing, not so sharp as to suggest pleurisy. In three of these nine cases there was some improvement in the symptoms of onset before the above symptoms appeared on the fourth or fifth day; in the rest, the course was continuous from the onset.

Pyrexia in these cases was rarely above 101° F. and was of irregular type:

it often consisted only of a rise to 99° or 100° once during the twenty-four hours. It generally subsided within eight days from the onset, and several days before the physical signs cleared.

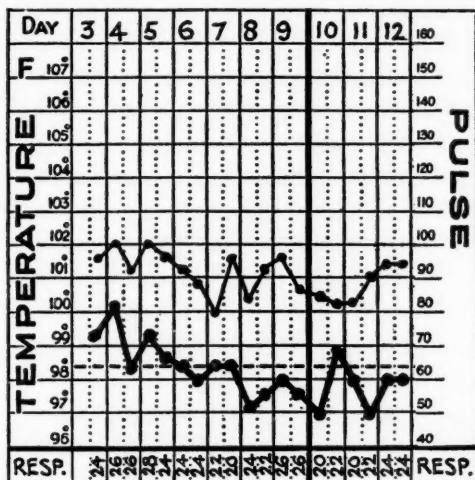
Areas of weak or 'suppressed' breath-sounds were the most characteristic physical sign, being observed in six of the nine cases. As they were among the earlier physical signs, and many of the cases were not seen before the end of the first week of their illness, they are probably common early signs. These areas usually occurred towards the bases, just below the angle of the scapula being a favourite site. They were constant in position at any one examination and were not influenced in any way by cough. They were of limited extent, never lobar. The percussion-note was not quite so resonant as elsewhere over these areas, and the voice conduction usually diminished. These signs were transient. In several cases, an area of suppressed breathing showed a return of the breath-sounds within one or two days, accompanied by moist inspiratory râles, which persisted for periods up to a week or 10 days. Other signs observed in this group, either accompanying or apart from 'suppressed' breath-sounds, were inconstant scattered rhonchi, heard most frequently in the axillae or at the bases, and scattered râles, which might be of various characters, and were sometimes transient, sometimes more persistent, especially at the bases.

In all these cases, radiological examination showed no change beyond, in some cases, a slight increase in linear striations such as is associated with bronchitis.

2. Six cases of group B were more severe. Of these, three occurred in patients who had a handicap to overcome: one was senile, one excessively obese, and the third was thirty weeks pregnant. In five, symptoms were continuous from the onset; in one only was there an intermission following the symptoms of onset. The symptoms in this sub-group were similar to those of the previous sub-group, but more severe. Complaint of pain in the chest was made in five of the six cases; it was not typically pleuritic in character, being uninfluenced by respiration. The pain was noted to be 'retrosternal on cough'; 'in the right side of the chest, not influenced by respiration'; 'in the back, especially in the region of the right scapula'; 'across the lower chest posteriorly'; and 'round the lower ribs on coughing'. The aspect of these more severely ill patients was often such as to suggest the presence of consolidation, tachypnoea and cyanosis being well marked; but this was excluded by radiological examination.

The signs at first were those of a generalized acute bronchitis involving bronchi of all sizes, down to the bronchioles, consisting of generalized rhonchi of varied pitch, with râles of varied extent. More or less marked dullness developed at one or both bases, accompanied usually by weak breath-sounds; and sometimes it was noted that the breath-sounds over these dull areas, while never losing their vesicular quality, became generally higher-pitched (see Case 5). The breath-sounds never acquired a bronchial quality in this group. In the cases with well-marked impairment of percussion-note

at the bases, it was common to find inconstant rhonchi anteriorly and at the apices posteriorly, with more constant râles during inspiration posteriorly over the dull bases; over these dull areas the voice conduction was always diminished. These signs suggested an oedematous sodden condition of the lung bases, short of actual consolidation. As the patients recovered, the physical signs usually retrogressed through stages in which



Case 1.

they were entirely similar to those noted in the less severe cases of Group B. A remarkable variation in the number and character of the râles from day to day was observed, especially in the stage of recovery.

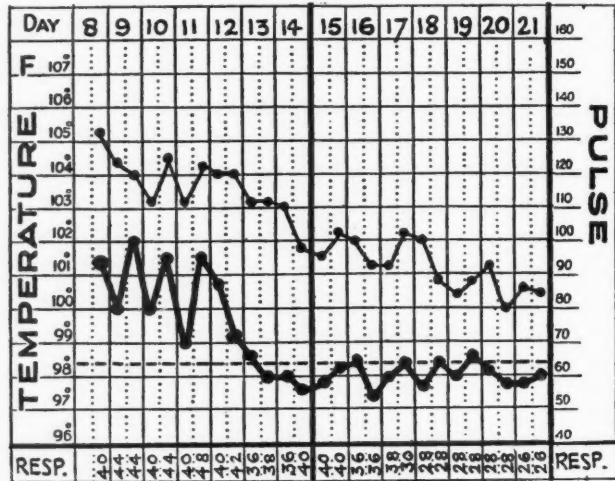
The pyrexia was similar to that of the milder cases, but usually more prolonged. It was of low irregular type, rarely above 101° F., and often bore little relation to the clinical condition and progress of the patient.

Case 1, Group B 1. Mrs. S. C., aged 34, housewife, was taken ill on December 27 with aching all over, frontal headache and increasing prostration, followed shortly by cough. On December 28 there was slight photophobia, the headache continued, and she had some soreness across the sternum on coughing; cough was dry. There was some dyspnoea, and she lost her appetite.

On admission to hospital on December 29 she was found to be somewhat obese; very flushed, sweating, with slightly cyanosed lips, and some dyspnoea on movement. Temperature 101° F., pulse 90, respiration 22. There was a small patch of herpes febrilis on the upper lip. The conjunctivae were glistening and the eyelids red and heavy. The fauces and soft palate were injected, but there was no exudate on the tonsils, and the posterior pharyngeal wall was dry, with prominent lymphoid follicles. On examination of the chest, a very definite area of 'suppression' of the breath-sounds was found at the right base; no added sounds were heard.

On the following day she appeared less flushed; the cough was troublesome and was accompanied by scanty purulent sputum. Dyspnoea was still

notable. On examination the chest showed a very definite change, numerous coarse râles with strong breath-sounds being audible over the area at the right base at which the breath-sounds had been weak on the previous day. A few fine râles were heard at the left base. Radiological examination on December 31 showed only a rather indefinite area of slightly increased bronchial shadowing in the inner portion of the right lower zone.



Case 2.

Low pyrexia, showing a rise to 99°–100°, persisted for five days in all; the cough persisted for twelve days, but was unproductive for the last few days, and the physical signs—râles at both bases, persisting longer at the right base—persisted for ten days in all.

The sputum on culture yielded *H. influenzae*, *Streptococcus viridans*, and *N. catarrhalis*.

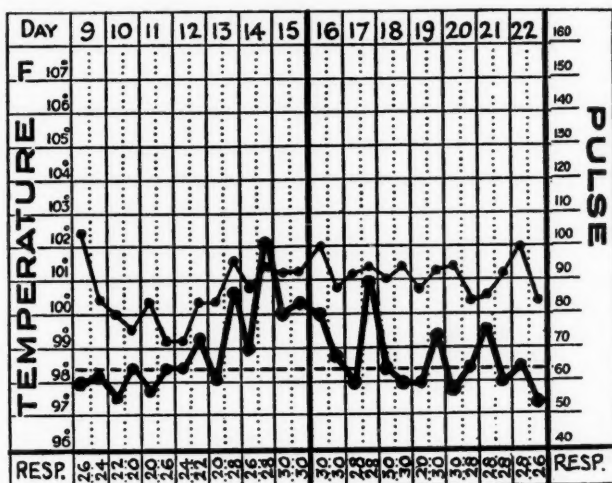
Case 2, Group B 2. Mrs. B. W., aged 31, housewife, was taken ill on December 30 with general malaise, feeling shivery, frontal headache, and aching in the limbs, shortly followed by cough. On December 31 she had to remain in bed, and some sputum accompanied the cough. By January 2 she felt a little better, and got up, but on January 3 she felt worse again, vomited, the cough was worse, and she had to return to bed. On January 4 pain across the lower part of the chest posteriorly and dyspnoea, even at rest, appeared. On January 6 she vomited again, the sputum was noted to be tinged with blood, and she was admitted to hospital. Two stepdaughters living in the same house had influenza at about the same time as the patient.

On admission she was noted to be very obese. She looked ill, flushed, slightly cyanosed, with gross tachypnoea. Temperature 102.4, pulse 128, respiration 68. The conjunctivae were slightly injected, but the fauces and pharynx showed no important changes. There was a moderate-sized general enlargement of the left lobe of the thyroid gland. This had been present for many years; the patient was born in Switzerland, and the goitre dated from adolescence. There were no signs of thyrotoxicosis.

The chest on examination showed numerous rhonchi of medium pitch

throughout both lungs, but more numerous anteriorly. There was moderate impairment of percussion-note at both bases; the breath-sounds, of weak vesicular character throughout, were weaker still at the bases, where a few crepitant râles were audible in addition to rhonchi.

On the following day slight improvement was noted. The respiration-rate was down to 45 per minute, and the colour improved.



Case 3.

On examination, the rhonchi were less numerous, but still scattered throughout the lungs, the impairment of percussion-note was much less, and was detected at the left base only, where there was a small patch of râles.

On January 8 the general condition was unchanged; a small patch of herpes febrilis appeared on the lips. X-ray examination showed no evidence of consolidation.

On January 10 there was some improvement, and the chest showed no impairment of percussion-note; a very occasional rhonchus only, but many fine râles at both bases, more numerous on the left.

On January 12 the temperature had come to normal by a rather steep lysis; the sputum, which had been frothy muco-purulent, with the mucoid element predominating, became more purulent. Examination showed slight impairment of percussion-note at the left base, with weak breath-sounds in this area, and scattered high-pitched rhonchi all over the chest. The amount of sputum rose to a maximum of 180 c.c. on January 14, and thereafter diminished rapidly. An occasional rhonchus was audible until January 19, when the cough was much diminished with only scanty mucoid sputum, and the chest showed no abnormal physical signs.

The sputum yielded a few *Streptococcus viridans* on culture, and on mouse inoculation caused late death with *Pneumococcus* type III.

Case 3, Group B 2. Mrs. E. F., aged 71, widow, was taken ill on December 24 with faintness, giddiness, aching in the limbs and lumbar region, vertical and occipital headache, sweating and shivering. On December 26 she developed a cough with purulent expectoration, with some pain behind the upper sternum on coughing. She stated that she was not

subject to winter cough. She had had pneumonia twice, in 1916 and in 1921. No known contact with influenza could be traced.

She was admitted to hospital on January 1, the ninth day of her illness. The aspect was rather apathetic but not otherwise remarkable: the fauces and pharynx showed no important change. The chest showed scattered medium to coarse rhonchi; it was noted that the strength of the breath-sounds varied from area to area. There was a moderate degree of arteriosclerosis; the pulse was of the collapsing type. B.P. 190/80. The aortic second sound was loud and musical.

X-ray examination (Plate 15, Fig. 1) revealed some increase in basal shadowing, but no evidence of consolidation, and some calcification in the aortic knuckle.

By January 4 she was feeling a little better; cough and purulent expectoration continued, and examination of the chest showed fewer rhonchi; there was slight impairment of percussion-note at the right base and axilla; numerous fine râles were audible over this area, and a few at the left base.

On January 5 she was not so well; looked apathetic, and said she 'felt lazy'. The impairment of percussion-note at the right base was more definite. Further radiological examination, however, showed no change.

On January 6 the temperature, which had settled, started to rise again. On examination the impairment of percussion-note at the right base was still more definite, the breath-sounds weak and accompanied by numerous coarser inspiratory râles, with no change in voice conduction. No rhonchi were heard. The sputum remained purulent, but consisted of small ragged pellets, remaining discrete in the fluid in the cup.

During the following week she remained in the same general condition, feeling tired and apathetic, the temperature assuming a swinging type to 102°. The physical signs remained much the same at the right base: sometimes a few scattered rhonchi were heard, and sometimes a few râles at the left base.

By January 15 she was improving and the temperature falling. The sputum was less in amount, still in discrete pellets but now homogeneous muco-purulent in character. Examination of the chest showed percussion change at the right base as before, with showers of fine inspiratory râles. Over the rest of the chest, especially posteriorly, scattered bubbling râles with occasional rhonchi were heard.

After this she remained afebrile: the cough persisted but the sputum became scanty and muco-purulent, then mucoid. The physical signs lingered on. On January 25 there was still slight impairment of percussion-note at the right base, with weak breath-sounds, and a few râles at the left base. On February 1 there were no abnormal physical signs, except a very few fine râles at the right base, and the patient was symptom-free.

Examination of the sputum on January 2 showed, on culture, *Streptococcus viridans*, *H. influenzae*, and *N. pharyngis*.

Case 4, Group B 2. Mrs. D. C., aged 31, housewife, was admitted to hospital on January 9. She was thirty weeks pregnant. On January 7 she had been taken ill with shivering and malaise and pain in the back and limbs. On January 8 she developed cough with pain in the midline of the back of the chest on coughing, extending to the right scapular region; vomiting occurred on this day, and there was also some temporal headache, and dyspnoea was noticed.

On admission she was very ill with severe dyspnoea, cyanosis, short dry

cough with the alae nasae working. The general aspect suggested a severe pneumonic condition. Temperature 100.2°, pulse 115, respiration 32. There was no notable abnormality of the fauces or pharynx. The chest showed limited respiratory excursion; percussion-note was moderately impaired at both bases posteriorly; the breath-sounds were vesicular throughout, weak at the bases with a curious high-pitched quality, but still of vesicular type; anteriorly scattered rhonchi and râles and posteriorly scattered rhonchi, with numerous râles over the impaired bases only, were heard. The râles were of coarse inspiratory type, the rhonchi short and high-pitched during expiration.

By the following day striking improvement had occurred; dyspnoea was much less, and there was no cyanosis. The physical signs, however, remained as before.

On January 11 the temperature was normal. Radiological examination (Plate 15, Fig. 2) showed no evidence of pulmonary consolidation.

By January 13 the impairment of percussion-note at the bases had cleared; the breath-sounds at the right base were rather weak, and were accompanied by numerous inspiratory râles, both posteriorly, in the axilla, and anteriorly.

By January 18 the only symptom was cough. Sputum, which had always been scanty, had disappeared, and the only abnormal physical signs found were a few rather coarser râles at the right base posteriorly.

By January 20 she was symptom-free and was discharged. Examination of the sputum showed *N. catarrhalis* and *Pneumococcus*, group IV, on culture.

C. Cases with Demonstrable Consolidation

There were 19 cases in this group, with seven deaths, a mortality of 37 per cent. (see Table III). They include one fulminating case which proved fatal within sixty hours of the onset of the influenza; this case will be described separately.

Among the remaining 18 cases a great diversity of anatomical types of lesion was observed.

1. In four the consolidation was of patchy distribution at both bases, and it was clear that the condition was essentially an extension of the bronchiolitis of Group B to a patchy broncho-pneumonia. Of these cases two died; one was aged 76 and the other had a localized old-standing bronchiectasis (Case 6). Cases 5 and 6 are examples of this type.

2. In nine a basal bronchiolitis or patchy broncho-pneumonia was associated with massive consolidation of one or more lobes. It was impossible to form any opinion whether the lobar consolidation had originated as such or as the result of confluence of broncho-pneumonic foci. In this group there were four fatal cases, all occurring in previously healthy individuals. Cases 7, 8, and 9 are examples of this type.

3. In four generalized bronchitis was associated with large patches of consolidation, best described as incomplete lobar consolidation; the extent of the consolidation being judged on the radiological appearance. No deaths occurred among these, of which Cases 10 and 11 are examples.

4. In one case only (Case 12) an isolated lobar consolidation was observed,

without evidence of other areas of broncho-pneumonia or of bronchiolitis. Occurring in a patient who gave a typical history of influenzal onset, and presenting those deviations of symptoms and signs from those usual in lobar pneumonia which were observed in the other cases in this series (see below), this case was regarded as showing equally good evidence of influenzal etiology.

TABLE III

Group,	Age.	Sex.	Duration to defervescence.	Day of onset of pneumonic symptoms.	Leucocytes.				Predominant organisms in sputum culture.
					Initial.	Day.	Maximum.	Day.	
C 1	36	F	14	4	14,000	6	21,000	11	<i>H. influenzae</i> , <i>Strep. viridans</i> <i>N. catarrhalis</i>
	36	M	14	4	18,000	8	18,000	8	<i>Strep. non-haem.</i> , <i>H. influenzae</i>
	44	F	10*	5	89,000	10	—	—	(P.M.— <i>H. influenzae</i>)
	76	F	17*	C	—	—	—	—	(P.M.— <i>Pneumococcus</i> gr. IV <i>H. influenzae</i>)
C 2	36	M	14	6	20,000	9	46,000	21	<i>H. influenzae</i> , <i>Strep. viridans</i>
	28	F	15	C	7,000	7	—	—	<i>Pneumococcus</i> gr. IV, <i>Strep. viridans</i> , <i>H. influenzae</i>
	32	M	21	14	14,000	17	—	—	<i>Strep. viridans</i> , <i>H. influenzae</i> <i>Strep. non-haem.</i>
	26	M	10	3	19,000	6	—	—	<i>Strep. viridans</i> , <i>Pneumococcus</i> gr. IV
	47	M	24	C	30,000	15	30,000	15	<i>Staph. aureus</i> , <i>H. influenzae</i>
	49	F	10*	4	10,000	7	—	—	<i>Pneumococcus</i> gr. IV
	50	M	8*						
	56	M	22*	14	62,000	17	129,000	19	<i>H. influenzae</i> , <i>Pneumococcus</i> gr. IV
C 3	57	M	16*	11	14,000	15	—	—	<i>Pneumococcus</i> type II Gram-neg. diplococcus
	48	M	14	5	30,000	11	30,000	11	<i>Strep. viridans</i> , <i>Pneumococcus</i> gr. IV
	66	F	11	C	18,000	3	18,000	5	<i>Pneumococcus</i> type III
	22	F	7	4	11,000	6	33,000	8	<i>Pneumococcus</i> types II and III
C 4	37	M	6	C	22,000	4	24,800	7	<i>Pneumococcus</i> gr. IV, <i>Strep. non-haem.</i> , <i>Staph. aureus</i>
	29	F	14	5	8,000	6	18,000	32	<i>Pneumococcus</i> type II
C (fulm.)	16	F	2½*	C	—	—	—	—	(P.M.— <i>Staph. aureus</i>)

* = Patient died on this day.

C = Course continuous from onset.

Onset. The time and mode of onset of the 'pneumonic' symptoms is of interest. In five cases the onset was insidious, being continuous with the influenzal symptoms. In ten the history was that about the fourth or fifth day of the influenzal attack the patient was feeling somewhat better, and might even have left his bed, when pleuritic pain heralded a return of his illness. This pain was accompanied by dyspnoea in six, and by a rigor in one. The actual day of influenzal attack on which these definite symptoms

of onset of pneumonia occurred was the third in one case, the fourth in five, the fifth in three, and the sixth in one. The mode of onset of the pneumonia had no obvious relation to the type of pneumonia nor to the subsequent course.

'Late' cases. In the remaining three cases the onset of pneumonic symptoms was much later, occurring on the eleventh day in one, and the fourteenth in two, with pain and dyspnoea in all three and rigor in two. These three patients all gave a clear history of the onset of influenza; they had struggled to carry on their normal activities in spite of feeling ill with anorexia and lack of energy, either without any initial period of rest in bed, or after a very short period of such rest.

The lung involvement in these three cases was of Group C 2; i.e. both massive lobar and patchy broncho-pneumonic consolidations. They were very gravely ill, and two of them died. They included the only two examples of apical consolidations in the series; in one of the fatal cases, lobar consolidations occurred in the right upper and left lower lobes, and in the patient who recovered, an isolated area of consolidation of the right lower lobe. In other respects, their clinical features were similar to those of the other cases of group C 2.

General aspect. The general aspect of the patients was different in several respects from that usually associated with primary pneumonias. They were apathetic and usually wished only to be left alone. In the less severe cases on questioning they said that they felt 'tired and lazy'. They looked tired, often with heavy, drooping, rather reddened eyelids. In most cases, there was a surprising absence of distress. Even the rapid respiration often observed did not cause distress; tachypnoea rather than dyspnoea was the rule. This was frequently accompanied by obvious cyanosis, and the combination of extreme cyanosis and tachypnoea with an apathetic lack of distress was most striking. In fatal cases, expectoration usually ceased towards the end, the patients making no attempt to cough. The distressing ineffective cough which usually occurs in asthenic subjects suffering from terminal pneumonia was seldom observed.

Physical signs. The physical signs in the cases presenting basal broncho-pneumonia were an extension of the signs observed in the more severe cases without consolidation. The inconstant scattered rhonchi and occasional râles observed in the cases without consolidation were also heard in these. The impairment of note at one or both bases was more marked, and sometimes was extreme. The breath-sounds were either very weak, or acquired a bronchial character in patches over the affected base. Typically, the presence of bronchial or tubular breath-sounds was inconstant, weak or distant sounds of this character alternating with silence or extremely weak vesicular sounds. The voice conduction over broncho-pneumonic areas might be unchanged, diminished, or most often was of a peculiar high-pitched quality, resembling aegophony. The râles over these areas varied from day to day, both in character and in number.

In cases where consolidation of the whole of a lobe was evident, the physical signs differed similarly from those usual with lobar pneumonia. This applied equally to those in which the lobar consolidation appeared to be the only pneumonic lesion, and those in which it might have been the result of confluence of lobular lesions. One of the most striking features of the physical signs was the extreme degree of dullness present over the consolidated lobe. Over the dull areas breath-sounds were either very weak, bronchial or tubular in character, or even entirely absent. The vocal resonance was usually of the aegophonic quality noted above; sometimes it might be entirely absent, or again it might be very little changed from normal. Added sounds were often absent or very inconspicuous at first over the areas of consolidation. With these lobar signs, signs of bronchiolitis or basal broncho-pneumonia at the opposite base co-existed, according to the type of case. It was noteworthy that the remarkably clear-cut physical signs associated with these lobar consolidations were present in all cases on the initial examination, usually on the first or second day after the onset of pneumonic symptoms; in contrast with the frequently delayed development of physical signs in primary pneumococcal pneumonia.

With the physical signs described above, suspicion of the presence of fluid naturally arose in cases with lobar consolidation. Consideration of the shape of the upper border of the dullness, which was often clearly limited to the surface-marking of the lobe, and of the position of the heart were sufficient in most instances to remove this suspicion, but in several cases, paracentesis was performed. In only one, a very thin layer of clear slightly blood-stained fluid was found and this did not accumulate further. No empyema occurred in the series.

A pleural rub was heard at the onset in two cases only. Herpes febrilis was observed in two.

Pyrexia. Cases with lobar consolidation tended to have higher temperatures than the rest, but the pyrexia was of irregular type, frequently swinging. No crisis was observed. Even a regular lysis occurred in one instance only, and this was the one showing lobar consolidation only (Case 12). The temperature was of the general type of that noted in Group B, but more prolonged. It was often remittent one day and sustained the next, without any obvious correlation with the clinical state of the patient.

The pulse-rate was in general in proportion to the temperature. In severely ill cases, the pulse was often of surprisingly good volume, and in fatal cases the blood-pressure was several times noted to be well sustained a few hours before death. No cardiac arrhythmias were observed.

Resolution. The process of resolution was slow in the cases with consolidation of lobar distribution, but more speedy in the others. In the broncho-pneumonic areas, while physical signs indicating persistent secretion in bronchioles and small bronchi might persist for ten to fourteen days after defervescence, the signs of consolidation, both clinical and radiological, cleared up rapidly. In cases with solid lobes the physical signs noted above

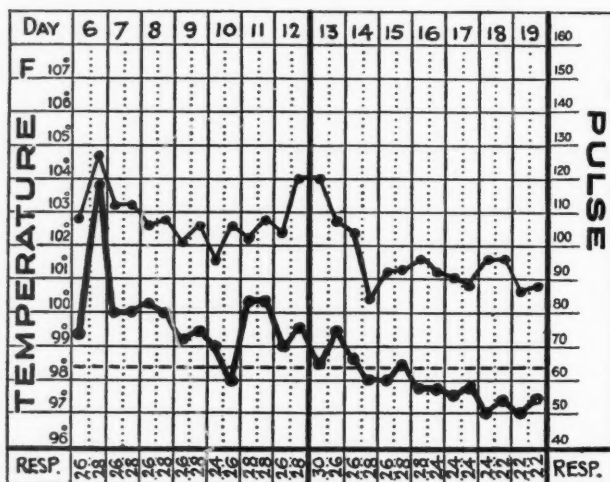
—marked dullness, variable weak or weak bronchial breath-sounds, and even aegophony persisted for long periods, in one case up to six weeks after defervescence. During the long persistence of these signs, added sounds of varying type were heard. Their variability was similar to that of the added sounds observed in the cases without consolidation; the râles tended to vary both in type and in number from day to day, though generally less numerous over still consolidated lobes. In several cases small localized areas of loud bronchial or tubular breath-sounds with increased voice conduction were heard for a short time during resolution; they were in marked contrast with the distant bronchial sounds and aegophony previously heard.

In only one case showing lobar signs was rapid resolution noted. This was that of a pregnant woman (Case 11). It seems likely that there was a considerable element of atelectasis of the lower lobes and that the descent of the diaphragm after delivery facilitated rapid re-expansion.

Sputum. The character and the amount of the sputum varied very considerably, and appeared to have no constant relation to the type of pneumonic lesion present. In frankly pneumonic cases it varied from scanty muco-pus to profuse pus. Typical 'rusty' sputum was never observed. In general, the production of much frothy muco-pus could be related to the presence of signs of generalized bronchitis. One type of sputum occurred frequently enough to be worthy of note, though its presence could not be correlated with any particular type of lung lesion. It was noted in about half the pneumonic cases, and also in some of those without consolidation (see Case 3). It consisted of rather ragged pellets of homogeneous purulent or muco-purulent material, from 1 to 2 cm. in diameter, which remained discrete, floating in the fluid in the sputum cup. It resembled the nummular sputum of chronic phthisical subjects, except that the individual pellets were more regular in size, smaller, and more homogeneous. This type of sputum usually appeared during the first week, and persisted into convalescence, gradually changing from purulent to mucoid in character, but remaining homogeneous and in discrete pellets. In the cases of Groups C 3 and 4, the sputum was scanty and muco-purulent, but in two of them was produced in similar discrete pellets.

Radiological appearances. The radiological changes appeared to lag behind the clinical signs in the broncho-pneumonic type, in which the picture was usually merely a coarse diffuse mottling of not very great density at the affected bases (Cases 5 and 6), showing no features differing from those of any other broncho-pneumonia. Similarly, in the cases of Group C 3, the areas of partial lobar consolidation showed no characteristic feature. The cases with massive consolidation of lobar distribution (Groups C 2 and 4) were distinguished by an unusual density of the shadows cast by the solid lobes (see Cases 7, 8, and 9). This appearance lent support to the clinical suspicion of fluid in several cases in which needling revealed none. Clearing of these very dense shadows was always slow.

Case 5, Group C 1. Mrs. N. F. aged 36, housewife, was taken ill on December 27 with chilly sensations and shivering, occipital headache, prostration and pains in the limbs and back, followed shortly by cough. On the following day, the throat was sore, and expectoration began. By December 30 she was feeling better, but on December 31 she was worse, the cough was more severe, she became dyspnoeic and had a pain in the chest in the midline anteriorly on coughing, extending to the precordium.



Case 5.

One of her children had influenza two days before the onset of her attack, and her husband was taken ill on the same day as herself: he was admitted to hospital on the day after her admission also with bilateral basal bronchopneumonia, and his illness was remarkably similar to hers throughout.

On admission to hospital on January 1 she was flushed with conspicuous cyanosis; there was no respiratory distress at rest, in spite of the cyanosis, but dyspnoea occurred on the slightest exertion. Temperature 99.2 °F., pulse 108, respiration 28. The tongue was dry; and the fauces were dry and injected, the pharynx dry and granular. The tonsils were fibrotic, but there was no exudate. The chest showed a few fine rhonchi anteriorly and at the upper part posteriorly; at the bases there was extreme dullness, more extensive on the left side, with weak breath-sounds on the right side, and a small patch of tubular breath-sounds at the angle of the left scapula. There were no added sounds over the dull areas; a few râles were audible at the upper level of the dullness on the left side. Radiological examination on the following day showed mottling at both bases with impaired translucency at the left base (Plate 15, Fig. 3).

On January 4 there was some improvement, but cyanosis was still present. About 50 c.c. of purulent sputum daily was being produced. On examination of the chest, numerous rhonchi were heard anteriorly; posteriorly the dullness at the bases was still present, but less than previously; the right base was still less dull than the left. Breath-sounds were weak at both bases with numerous fine to medium inspiratory râles.

On January 5 there was pleuritic pain in the left axilla, extending to the

upper abdomen and also in the left trapezius ridge, suggesting affection of the diaphragmatic pleura, but no change in the physical signs.

By January 7 the pain was present only in the shoulder. Cough was frequent and was accompanied by sputum in small ragged purulent pellets. On examination the rhonchi had cleared; dullness at the bases was still present but less extensive; the breath-sounds were weak at these areas, with a few fine râles extending into the axilla on the left side. On the following day, the râles were noted to be coarser in quality.

By January 11 the temperature had settled. Sputum was less in amount, but still of the same nature. Little change was noted in the physical signs, except that the impairment of note at the bases was less.

By January 15 the impairment of note at the bases was no longer observed; there were some râles at both bases with somewhat weak breath-sounds at the right base. Until January 26 fine inspiratory râles were audible at times at the left, and less often at the right base: on one occasion coarse rhonchi were heard at both bases. The improvement in her general condition was very gradual; expectoration ceased on January 20, but cough persisted for some days longer.

The sputum, cultured on January 2 yielded non-haemolytic streptococci and *H. influenzae*.

Case 6, Group C 1. Mrs. B. K., aged 44, was taken ill on December 28 with frontal headache, shivering, pain in arms and legs, and took to her bed. On January 3 cough and pain in the left side, with dyspnoea, began. On the following day she tried to get up, but felt too weak. Her husband had a similar illness at the same time.

She was admitted to hospital on January 6, desperately ill and collapsed, pale, grey, cyanosed, and sweating. Temperature 100.2° F., pulse 150, respiration 40. The fauces and pharynx showed no distinctive feature; imperfectly expectorated sputum adhered to the pharynx. The chest showed very numerous rhonchi and coarse râles, largely obscuring the breath-sounds, but these appeared to be somewhat higher-pitched on the right side, though still vesicular. The percussion note was relatively impaired over the whole of the right lung and at the left base. Radiological examination (Plate 15, Fig. 4) showed scattered coarse mottling, especially at the left base.

She steadily went down hill and died on the following day.

Autopsy. The important findings were confined to the respiratory system. There was a congestion of the lower part of the trachea, with generalized purulent bronchitis. A localized old bronchiectasis was present in the middle of the left lower lobe. There was generalized severe bronchiolitis, with two or three foci of broncho-pneumonia at the right base, but no other consolidation.

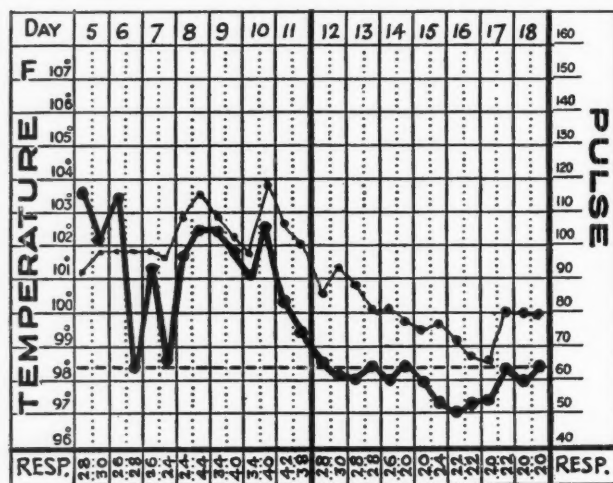
Histologically, the lesion was mainly an intense suppurative bronchiolitis with widespread albuminous exudate in the alveoli; but even in the absence of exudate in the alveoli, in places there was purulent infiltration of the alveolar wall—i.e. evidence of interstitial pneumonia. The presence of some broncho-pneumonia in the right lower lobe was confirmed.

Culture from the lung showed *H. influenzae*.

Case 7, Group C 2. W. E., male, aged 36, was taken ill on December 27 with shivering, feeling ill, headache, sweating, dry uncomfortable throat, and cough. On December 31 he returned to his work, but on January 1 he

had a severe pleuritic pain in the right side of the chest extending to the upper abdomen, with dyspnoea.

He was admitted on January 1 very flushed, slightly cyanosed, dyspnoeic, and sweating. Temperature 103.8°F. , pulse 90, respiration 28. The conjunctivae were injected, the eye-lids heavy, and the eyes watering. The fauces and pharynx showed no notable change. The chest showed absolute



Case 7.

dullness over the lower lobe of the right lung, extending round into the axilla and the lower part of the chest anteriorly. Over this area the breath-sounds were absent and the vocal resonance diminished. No added sounds were audible except a few rhonchi at the left base. Consideration of the shape of the upper border of the dullness, which started posteriorly at about the third rib and extended obliquely downwards and forwards made it unlikely that there was any considerable collection of fluid.

Very little change occurred in the symptoms in the next few days; pain in the right side remained severe. The sputum was muco-purulent. By January 4 a small area of weak bronchial breath-sounds was found at the angle of the right scapula, and dyspnoea was greater, the respiration-rate having risen to 40.

Radiological examination (Plate 16, Fig. 5) on January 4 showed an extremely dense shadow obscuring the lower two-thirds of the right lung field. Paracentesis on this day failed to find fluid.

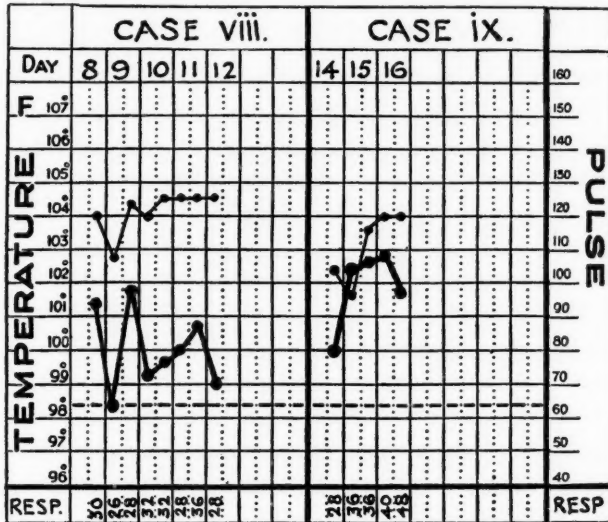
On January 7 it was noted that the sputum consisted of 'rather glairy muco-purulent blobs', and although the symptoms had not changed, the physical signs had altered considerably. There was a new area of dullness at the left base. Over the dull areas on both sides the breath-sounds were weak, especially on the right side, and there were very numerous mixed medium and bubbling râles.

On the following day the temperature had fallen to normal, but some cyanosis persisted. The chest showed fewer râles, of much finer quality, over the dull areas, with scattered rhonchi elsewhere. Very weak tubular breath-sounds were heard over the right base posteriorly, and bronchial

breath-sounds over the dull area at the lower part of the right chest anteriorly: this seemed to indicate consolidation of the right middle lobe.

On January 9 paracentesis in two spaces produced only a few c.cm. of slightly blood-stained clear fluid, which was sterile on culture.

By January 12 cyanosis had disappeared but there was still some dyspnoea on movement. Much sputum in purulent pellets up to 2 cm. in diameter



Cases 8 and 9.

was being produced. The area of dullness on the right side had diminished in extent anteriorly. The breath-sounds were absent and there was aegophony over this area. At the left base, some coarse râles were heard.

The evidence of consolidation of the right base persisted: on January 18 a skiagram showed complete opacity of the lower half of the right lung persisting. On February 2 there was still dullness at the right base, extending round into the axilla, with generally weak or absent breath-sounds, but one small area of weak tubular sounds, and aegophony; a few râles over the upper part of the dullness on the right side and also at the left base. The sputum was much diminished in amount, but retained the character of discrete homogeneous muco-purulent pellets.

On February 13 a skiagram (Plate 16, Fig. 6) showed much clearing, but still an area of quite dense opacity at the right base.

On February 16 cough still persisted, with similar sputum; some pleural friction was noted at the right base. He was allowed up for the first time on this day. On discharge on March 1 he was symptom-free, but still showed impaired percussion note at the right base with weak breath-sounds and diminished vocal resonance.

Culture of the sputum on January 2 showed *H. influenzae* and *Streptococcus viridans*.

Case 8, Group C 2. Mrs. N. P., aged 44, housewife, was taken ill on December 25 with aching in the back and limbs, shivering, vomiting, and left-sided headache with ear-ache. The throat was uncomfortable and dry,

there was some aching behind the eyes with watering eyes and photophobia. She developed cough with purulent sputum on December 27. On December 28 she got up, but had to return to bed on account of stabbing pain in the right side, dyspnoea and occasional vomiting.

There was a previous history of right-sided pleurisy in 1920. One home contact developed influenza a few days after the patient.

She was admitted to hospital on December 31 very flushed with generalized cyanosis, sweating slightly and dyspnoeic. Temperature 101.4° F., pulse 120, respiration 30. The conjunctivae were injected, the eyelids red and swollen. The fauces were slightly injected, the pharynx not remarkable. On examination of the chest, there was complete dullness over the right lower lobe, extending round into the axilla; the note was impaired at the left base. Over the dull area, breath-sounds were absent, and there was aegophony over the whole of this area. No added sounds were heard. There was no cardiac displacement; the blood-pressure was 178/98.

No change was noted on January 2. Radiological examination (Plate 16, Fig. 7) showed dense consolidation in the right middle and lower zones. On January 3 cyanosis was more marked. Cough was troublesome, but sputum amounted only to 20 c.c. daily. Very little change was noted in the physical signs, except that the dullness, if anything, was even more marked. Paracentesis failed to find fluid.

On January 4 she was tachypnoeic but drowsy; very cyanosed, but a better colour after she had been aroused. Cough was less. The physical signs had extended, numerous rhonchi being audible all over the lungs anteriorly, with a few râles: the areas of dullness had become intensified and more extensive at both bases: the breath-sounds were weak at the left base, and absent at the right base, except for a small area at the angle of the scapula where distant bronchial sounds were heard. No added sounds were audible over the dull areas.

She died quietly, the pulse remaining good up to the end; the blood-pressure a few hours before death was still 160/75.

The sputum yielded *Pneumococcus* Group IV in pure culture.

Autopsy. The trachea showed extreme congestion, especially in its lower half, and extending into the main bronchi. The right pleura was covered with a fibrino-purulent exudate, but very little fluid, and there was a little fibrinous exudate over the left lower lobe.

The right lower lobe was consolidated throughout, resembling early grey hepatization. The basal one-third of the left lower lobe showed similar consolidation except for some haemorrhage.

Histologically, there was acute interstitial inflammation in the alveolar walls and finer connective tissue septa, with acute arteritis as a striking feature. The alveoli were filled with polymorphs and varying proportions of mononuclear cells and fibrin. Very occasionally necrosis of alveolar walls was seen. Some alveoli and their ducts were greatly over-distended.

Case 9, Group C 2—'late' pneumonia. H. F., male, aged 57, carpenter, was taken ill on December 29 with generalized headache, pains in the limbs, anorexia, pain in the pit of the stomach, and cough. He carried on with his work until January 8, when he vomited and felt shivery; the cough became worse, and was accompanied by severe substernal pain, later spreading round to the side of the chest.

He was admitted on January 11. Temperature 100° F., pulse 104, respiration 28. He looked ill, flushed but not cyanosed, dyspnoeic on

movement, very apathetic and drowsy. There was slight ptosis of the left eyelid. The conjunctivae were injected with excessive lachrymation. The fauces and pharynx were slightly injected. The chest showed marked impairment of note at the right base, and slight impairment, less extensive, at the left base. Breath-sounds were weak at the right base, with numerous mixed râles; a few râles were heard at the left base. The pulse was of good volume, blood-pressure 100/60.

On the following day, he appeared even more prostrated; the dyspnoea was increased and there was definite cyanosis. The ptosis was more obvious, and now bilateral, left side more than the right; the ocular movements and pupil size and reactions were normal. The chest signs were little changed; dullness more marked, fewer râles.

Radiological examination (Plate 16, Fig. 8) showed irregular consolidation of the middle and lower zones of the right lung, and relative want of translucency of the lower zone of the left lung.

On January 13 he was very quiet and apathetic, and the cough had almost ceased. Generalized rhonchi were noted; the areas of dullness at both bases had extended, and there were for the first time distant bronchial breath-sounds at the right base, and a small patch of weak tubular sounds at the left base. He died at 1 a.m. on January 14.

Culture of the sputum yielded *Pneumococcus* predominating and Gram-negative diplococci. Mouse inoculation yielded *Pneumococcus* type III.

Autopsy. Slight congestion of the lower trachea and bronchi. The right lower lobe showed early grey hepatization, except for a narrow strip at the anterior margin. There was similar consolidation in the lower posterior two-thirds of the right upper lobe with early suppuration at one point. There was red consolidation of the lower and posterior part of the left lower lobe. The rest of both lungs was congested; there was fibrinous pleurisy over the consolidated parts.

Histologically, the picture was that of grey hepatization with a large minority of the alveoli showing very few cells though filled with fibrin. In places, a very distinct acute interstitial change was present in the alveolar walls and around small vessels. In the left lower lobe there was haemorrhage in many alveoli. Bronchiolitis was prominent throughout.

Case 10, Group C 3. P. M., male, aged 37, was taken ill on January 12 with general weakness, noticed on rising in the morning, pains in the limbs and back, and severe frontal headache. He had to return home from his work and fainted on the way. That night he vomited repeatedly. On January 13 cough began, with pain in the lower part of the right axilla. Vomiting continued.

On admission to hospital, January 14, he was slightly flushed, sweating, and dyspnoeic on slight exertion: there was no cyanosis. Temperature 100° F., pulse 100, respirations 28. Herpes febrilis was noted on the lower lip. The fauces were injected, the tonsils fibrotic but not otherwise abnormal. The chest showed some impairment of note over the lower half of the right lung posteriorly with weak breath-sounds and fine râles; in the left axilla there was an area of weak breath-sounds with râles.

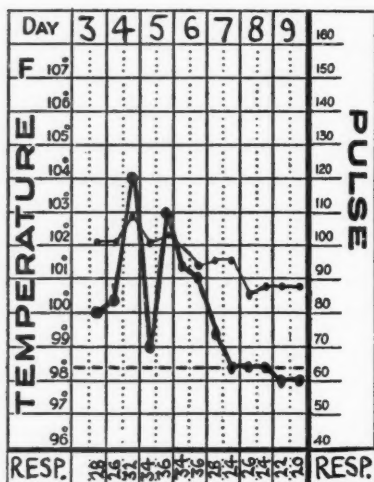
Radiological examination (Plate 17, Fig. 9) of the chest on January 16 revealed consolidation in the right lower zone.

On January 18 the symptoms were unchanged. Sputum was profuse and muco-purulent. On examination of the chest, the impairment of percussion-note at the right base was more marked, and there was slight impairment

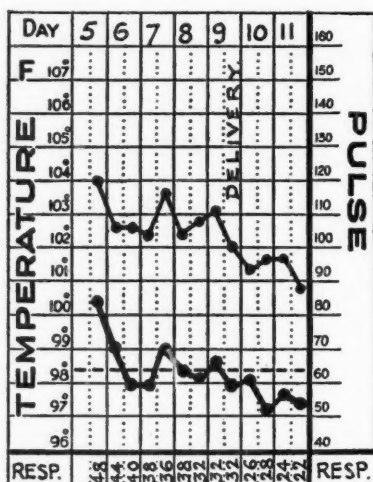
in the left axilla. The breath-sounds were weak at the right base and the left axilla; scattered rhonchi were heard all over the chest, with fine râles at the right base and axilla.

The temperature fell to normal on January 19.

On January 21 slight epistaxis occurred. The generalized rhonchi had cleared; impairment of note at the right base was less, but breath-sounds



Case 10.



Case 11.

in this area were still weak and accompanied by fine râles. In the left axilla, the breath-sounds were still weak, and an occasional soft rhonchus was heard at the left base.

Further radiological examination (Plate 17, Fig. 10) on January 27 showed the shadow previously noted to have disappeared; occasional râles were still audible at times at the right base and left axilla, but he was symptom-free.

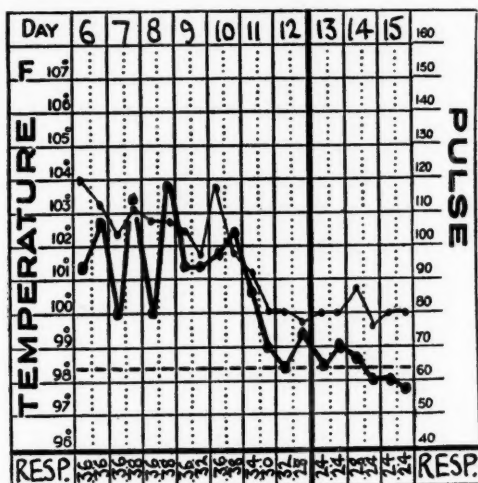
Culture of the sputum on January 16 produced *Pneumococcus* group IV, non-haemolytic streptococci, micrococci and *Staphylococcus aureus*.

Case 11, Group C 3. Mrs. A. C., aged 22, thirty-six weeks pregnant, was taken ill on the night of January 2, with a rigor, malaise, vomiting, and sweating. She had had a slight 'cold in the nose' since December 30. On January 3 there was some aching in the lumbar region. She was feeling better on January 4, but on January 5 she felt worse with pains in the limbs and back. On January 6 cough began, associated with severe pain in the left side of the chest and dyspnoea.

She was admitted on January 6 obviously ill, flushed, cyanosed, dyspnoeic and sweating slightly. Temperature 100.4°F. , pulse 118, respirations 44. The only notable physical signs were in the chest. There was dullness at the left base posteriorly, and impairment of note over the right middle lobe anteriorly. Breath-sounds were tubular over the dull area at the left base, and doubtfully bronchial over the right middle lobe. No added sounds were heard.

Radiological examination on January 8 (Plate 17, Fig. 11) showed consolidation of both lower lobes.

There was little change until January 9 when she looked better, with less cyanosis and dyspnoea, but complained of severe pleuritic pain on the right side, with increased cough. The sputum consisted of small pellets of rather glairy muco-purulent material, remaining discrete when floating in fluid. Examination showed considerable extension of the physical signs, in spite of the improvement in the general condition. There was complete



Case 12.

dullness at both bases, and over the right middle lobe. Breath-sounds were tubular at the left base, weak broncho-vesicular over the right middle lobe, and weak vesicular over the right lower lobe. The only added sound was extensive coarse pleural friction at the right base.

On January 10 she went into labour; delivery was assisted with forceps, and the child was healthy, weight 5½ lb.

Great improvement followed. On January 11 she was coughing less: pain in the right side still present but not severe. On examination, the dullness at the left base was less extensive: that at the right base was unchanged, but there was normal resonance over the right lower lobe, and there was a localized patch of tubular breath-sounds at the angle of the left scapula, with aegophony. Fine râles were audible over both lower lobes and the right middle lobe.

On January 11 further improvement was noted. Sputum was reduced to three or four purulent pellets daily. The dullness at the bases was less extensive: the small area of tubular breath-sounds at the left base persisted, but the sounds at the right base were weak vesicular.

By January 18 she was symptom-free, and a few fine râles at both bases after cough were the only abnormal physical signs. A skiagram showed no abnormality on January 23, confirming the completeness of this rapid resolution.

Sputum culture yielded *Pneumococcus* types II and III, *Streptococcus viridans* and micrococci.

Case 12, Group C 4. Nurse W., aged 28, was taken ill on December 31 with frontal headache, pains in the limbs, and watering eyes, followed by

cough with scanty purulent sputum. She carried on with her work until the evening of January 4 when she developed a pain in the left side of the chest, with dyspnoea, and her cough was worse.

She had had pneumonia five years previously.

She was admitted on January 5; temperature 101.4° , pulse 120, respirations 36; dyspnoeic, flushed, slightly cyanosed and sweating. She was noted to be 'very quiet'. Abnormal physical signs were confined to the chest, where there was complete dullness over the left lower lobe, with distant tubular breath-sounds over this area. No added sounds were heard.

She was kept in an oxygen tent until January 11. Throughout this time little change occurred in the physical signs; no added sounds were heard at any time. Towards the end of this time, on two examinations, weak tubular breath-sounds were heard at the right base next to the spine; these were probably conducted. Cyanosis was less, and the pulse slowed on her transference to the tent. She was noted to be 'very quiet except in paroxysms of cough'. The sputum was scanty, rather glairy muco-purulent in character. From January 8 to January 11 the temperature gradually fell, and a slow improvement occurred.

On January 11 the extreme dullness at the left base, now accompanied by absence of breath-sounds and aegophony, led to suspicion of fluid, which was not confirmed by a skiagram (Plate 17, Fig. 12). These physical signs cleared only very slowly; on January 20 there was still impairment of percussion-note at the left base with a small area of tubular breath-sounds now accompanied by markedly increased vocal resonance, in the left inter-scapular region.

She was discharged on February 6, a further skiagram showing only some general want of translucency at the left base.

Pneumococcus type II, was demonstrated in almost pure culture in the sputum.

Fulminating Pneumonia

Only one case was observed.

Case 13, Group C. K. O., female, aged 16, laundry assistant, returned home from work on January 2, with frontal headache, backache, and lassitude. On the following day she felt shivery and flushed, cough causing pain in the chest began, and she vomited in the evening.

On January 4 the pain was more severe, and she complained of sore throat. She was noticed by her relatives to be breathing fast and to be grey in colour.

She was said to have had rheumatic heart disease at the age of 12; her mother had been treated for pulmonary tuberculosis. No special contact with influenza was known.

On admission to hospital on the evening of January 4 she was desperately ill, very dyspnoeic with greyish pale cyanosis, collapsed, and sweating slightly. Temperature 103.8° , pulse 140, respirations 60. The fauces were slightly injected, tonsils not notable, pharynx dry, with prominent lymphoid follicles. Examination of the chest showed scattered rhonchi anteriorly; posteriorly there was extensive dullness at the right base, and less extensive dullness over the upper part of the left lower lobe; over the right base distant tubular breath-sounds were heard, and over the dull areas at the left base bronchial breath-sounds, with weak vesicular sounds elsewhere. No added sounds were heard posteriorly. The heart showed a tic-tac rhythm with no murmurs. Blood-pressure 102/68.

Little improvement in colour was caused by administration of oxygen by nasal catheter, and she died at 2 a.m. on January 5, approximately sixty hours from the onset of the influenzal attack.

Autopsy. The chief findings were as follows: necrotizing tracheitis and bronchitis. Both lower lobes showed haemorrhagic consolidation, less complete at their apices. There were also small patches of consolidation in the right upper lobe. There was slight fibrinous pleurisy, with a small exudate in the right pleura.

Histologically the lesion appeared to be a necrotizing bronchiolitis and 'alveolitis' with haemorrhage stuffing the alveoli in infarct-like fashion; it might be described as an acute interstitial pneumonia with necrosis. In limited areas there were small abscesses about 2-3 mm. in diameter; in these especially, but also throughout the affected areas, there were numerous small groups of Gram-positive cocci.

Culture from the lung yielded *Staphylococcus aureus*, and the influenza virus was isolated from the lung by Dr. Andrewes.

Pathological Features of the Lungs in Fatal Cases

Certain distinctive features appeared in the histological picture of the lungs. Tracheal and bronchial inflammation with epithelial desquamation was prominent, and in some cases amounted to a necrotizing process. Evidence of interstitial inflammatory reaction in the form of infiltration of the interstitial tissues with inflammatory cells could be found in places in all cases; in some there was evidence of actual necrosis of alveolar walls, which had given rise to haemorrhage. In some the alveolar exudate tended to be albuminous rather than fibrinous.

These changes were most well-marked and extensive in the fulminating case. The two fatal cases of Group C 1 showed mainly an intense suppurative bronchiolitis, with some interstitial pneumonia as well as more or less extensive broncho-pneumonia. The four fatal cases of Group C 2 fell pathologically into two groups, which corresponded with the clinical distinction between the 'early' and 'late' pneumonias; in the former the features noted above could be distinguished easily, though elements of the usual picture of lobar pneumonia with fibrinous alveolar exudate were present, while in the latter the picture more nearly resembled that of lobar pneumonia, though evidence of interstitial inflammation and bronchiolitis could be detected.

I am indebted to Dr. J. Gray for the above brief pathological notes; a complete account of the pathology of the fatal cases of this series is shortly to be published by him.

Blood Picture

White-blood counts were made as far as possible every other day throughout the stay of patients in hospital. A red-blood count was done at the first count only.

The normal white-cell count by the method used has a mean value of

8,000 per c.mm. with a calculated possible variation of 2,000 to 14,000 per c.mm. Differential counts were made on dried films, 200 cells only being counted. This is sufficient to show any marked change in the distribution of cell types, but insufficient for the detection of small alterations.

The main features of the total white counts are shown in Tables I, II, and III, where the first count done in each case and the maximum count in those cases which were followed are shown, together with the day of the disease on which these counts were observed.

The following observations can be made:

1. Grouping together Groups A and B 1, a normal white-cell count was found in every case at the first count. From the twelfth to the seventeenth day leucocytosis from 15,000 to 30,000 was found in half the cases followed. Most of the cases of Group A could not be followed, as they left hospital after a few days; but the incidence of this 'convalescent' leucocytosis seemed to be about equal in Groups A and B 1, judging from the counts made on the few cases of Group A which were followed. That such a leucocytosis is not constant is shown by the fact that it was not found in one patient followed for twenty-two days.

2. In Group B 2 leucocytosis occurred earlier, but still was not observed before the ninth day.

3. In Group C leucocytosis was observed in seven cases before the ninth day, and it might be observed as early as the third day. The count reached higher levels in this group than in any other; it is interesting to note that the two cases which showed the highest counts—129,000 and 89,000 per c.mm.—were both fatal, and *H. influenzae* was demonstrated by culture from their lungs. Also in the case showing the next highest count, 46,000 per c.mm., this organism was predominant in the sputum-culture.

4. The leucocytosis, when present, was due to an increase in the polymorphs, and no other alteration was found in the differential white-cell count. In a pneumonic case which recovered without leucocytosis in the early stage proleucocytes were present.

I am indebted to Dr. Janet Vaughan for these haematological observations.

Bacteriology of the Sputa

I am indebted to Dr. A. A. Miles and Dr. F. D. Johnstone for the following bacteriological data and their analysis.

Sputum examination consisted of (a) direct examination of a stained smear, (b) seeding a loopful of sputum on to two blood-agar plates, and in some cases (c) intraperitoneal inoculation of a mouse with 0.5 c.c. of an emulsion of the specimen in peptone water. It may be said at once that the direct examination, after excluding the presence of acid-fast bacilli, yielded no information that indicated the subsequent results of culture or mouse inoculation, except in two sputa that were microscopically and culturally proved to be infested with a yeast, and a few sputa full of small

Gram-negative bacilli, which on cultivation proved to be *H. influenzae*. The plate cultures were examined after twenty-four hours at 37° C., and the bacteria isolated and identified were ranked according to their predominance. In addition to characteristic individual and colonial morphology, the following criteria were adopted for the naming of each type of bacterium.

Streptococcus haemolyticus: β -haemolytic, McLeod's test for soluble haemolysin positive. Pseudo-haemolytic streptococci: β -haemolytic, McLeod negative, bile insoluble. Pneumococcus: α -haemolytic, McLeod negative, bile soluble; Types I, II, and III agglutinated by homologous type antisera, and Group IV those not agglutinated by Types I, II, and III antisera. *Streptococcus viridans*: α -haemolytic, McLeod negative, bile insoluble. Non-haemolytic streptococci: bile insoluble; identified as *Streptococcus faecalis* if heat resistant and mannite fermenting. *Staphylococcus aureus*: golden pigment, mannite fermentation and relatively rapid liquefaction of gelatine. *Staphylococcus albus*: white colonies, no fermentation of mannite, and slow gelatine liquefaction. *H. influenzae*: failure to grow on nutrient agar, satellitism on blood-agar in vicinity of a staphylococcus colony.

The Gram-positive micrococci and diphtheroids were identified on morphology and colony form alone. The Gram-negative cocci were separated on colony form into *N. catarrhalis* and *N. pharyngis* types, and the former identified if necessary by its non-fermentation of glucose, maltose, and sucrose in serum water. Coliforms, &c., were identified by the usual biochemical tests.

The gross results of cultivating 53 sputa from 47 influenza patients were tabulated, the organisms being ranked in order of their abundance on the plates.

When these results were divided into three groups, A, B, and C, corresponding with the clinical classification of the cases, certain differences between the groups became apparent. Many types appeared in tables as predominant organisms which are seldom directly associated with lung disease, or which are, like *Streptococcus viridans*, part of the normal mouth and throat flora. If the pseudo-haemolytic and non-haemolytic streptococci, *Streptococcus viridans*, diphtheroids, and Gram-positive micrococci are assumed to be non-pathogens, and disregarded, the remaining types may be re-ranked in order of abundance with the result shown in Table IV. Under this treatment some sputa are negative (i.e. yielding no pathogens on culture). In this event a positive result from mouse inoculation is entered in the table, and the bacterium isolated from the heart-blood of a mouse dead from sputum inoculation is ranked as number one. This procedure seems defensible on the following grounds. Mice were not inoculated with influenzal sputa as a routine procedure, but during the period 22.12.36 to 9.2.37 forty-four mice were inoculated with sputa from cases of acute lung disease from various hospital wards. Concordance between plate and mouse result were obtained in 28 sputa. Thirteen sputa, yielding no pathogens on plate culture, killed mice with septicaemias due to Types I,

II, and III, and Group IV pneumococci, *H. influenzae*, and in one case *Streptococcus haemolyticus*, Lancefield's Group A. In only three sputa was a positive plate culture (two Group IV pneumococci and one *H. influenzae*) not followed by death of the mouse. In about 94 per cent. of sputa, therefore, the mouse test confirms or amplifies the culture test, and has been counted as a culture test when the plates have been negative.

TABLE IV
Analysis of Predominant Bacteria in Sputum Cultures from the Present Series, Omitting Non-pathogenic Organisms.

Group.	Number of cases.	Number of sputa.	Number of sputa yielding positive result.	Rank.	Pneumococcal types.				Pneumococcus.	<i>Strep. haemolyticus</i> .	<i>Staphylococcus</i> .	<i>H. influenzae</i> .	<i>N. catarrhalis</i> or <i>pharyngis</i> .	Miscellaneous pathogens.
					I	II	III	IV						
A	8	8	8	1 2	— —	— —	— —	— —	— —	2 1	1 —	3 —	1 —	
B	22	23	21	1 2	— —	— 1	1 —	3 1	4 2	— 1	1 1	6 2	9 2	1 yeast
C	17	22	21	1 2	— —	3 —	4 —	5 2	12 2	— 2	2 —	6 3	1 1	1 yeast
Total	47	53	50	1 2	— —	3 1	5 —	8 3	16 4	2 3	2 1	15 5	11 3	2 yeasts

The modified ranking in Table IV reveals striking differences between Groups A, B, and C. Pneumococci appear in Group B and predominate in C. Gram-negative cocci, mainly of the *catarrhalis* type, appear in large numbers in Group B and sink into insignificance in Group C. The influenza bacillus appears with about equal frequency in all three groups.

There were no characteristic associations of bacteria in these sputa, and compared with contemporary sputa from non-influenzal hospital patients there was nothing to mark them as peculiar, either in microscopic appearance or in the results of plate culture.

In addition to the influenzal sputa listed above, 96 sputa were cultivated in the bacteriological laboratory in the period 22.12.36 to 9.2.37. These have been analysed in a similar manner, and divided into three groups by consideration of clinical data: (a) probably influenzal, though not included in this series, (b) possibly influenzal, the clinical diagnosis being doubtful, and (c) non-influenzal. This last group includes sputa from patients with various acute and chronic pulmonary and bronchial infections, asthma, neoplasms of the lung, &c. Table V shows the result of this analysis. It will be seen that none of these distributions differs significantly from that of the present series as a whole, given in the last section of Table IV; indeed, the resemblance between the non-influenzal group and the present series is striking.

Since a number of sputa forming Group A came from cases early in the epidemic, the variations in bacterial flora within the influenzal group might reflect only a difference in the prevalence of types in the sputal flora of the hospital at Christmas as compared with January and February, when a large number of the cases contributing to Groups B and C occurred. An analysis was made of the bacterial-type frequency distributions of non-

TABLE V

Analysis of Predominant Bacteria in Sputum Cultures from Other Cases at Hammersmith Hospital, 22.12.36-9.2.37, Omitting Non-pathogenic Organisms.

Group. (Clinical classification.)	Number of cases.	Number of sputa	Number of sputa yielding positive result.	Rank.	Pneumococcal types.				Pneumococcus	<i>Strep. haemolyticus</i> .	Staphylococcus.	<i>H. influenzae</i> .	<i>N. catarrhalis</i> or <i>pharyngitis</i> .	Miscellaneous pathogens.
					I	II	III	IV						
Influenzal, but not included in present series	7	11	9	1	—	—	—	3	3	—	—	6	—	1 yeast
				2	—	—	—	1	1	—	1	—	1	
				3	—	—	—	—	—	—	—	—	1	
Possibly in- fluenzal	20	25	22	1	1	—	1	5	7	2	2	6	4	{ 1 Gram-neg. bacillus 1 yeast
				2	—	2	—	1	3	1	2	3	2	
				3	—	—	—	—	—	1	—	1		
Non-influenzal	54	60	45	1	4	1	3	11	19	3	2	14	9	{ 1 <i>B. friedländer</i> , 1 yeast, 1 <i>B. coli</i> , 1 <i>B. aerogenes</i>
				2	—	—	1	6	7	1	2	1	9	
				3	—	—	—	—	—	1	1	1	1	

influenzal sputa examined between 22.12.36 and 5.1.37; 6.1.37 and 22.1.37; and 23.1.37 and 9.2.37. There were 21, 17, and 28 sputa in each period respectively, and the type distributions were alike in all three.

The bacteriological evidence therefore shows that the bacteria associated with the influenzal epidemic were those locally prevalent in respiratory infections. Analysis of the data of the present series according to the clinical classification, shows significant differences in the bacterial type distribution in the various groups. The association of pneumococci with the 'pneumonic' Group C, and possibly of *N. catarrhalis* with the 'bronchitic' Group B, suggests that bacteria tend to be associated with lesions of similar general type in both influenzal and non-influenzal cases.

Correlation of the Clinical and Pathological Data

Group A is characterized by pharyngitis and tracheitis. Cough with retrosternal pain, without signs of bronchitis, is sufficient to justify the diagnosis of tracheitis. It is true that some of the cases included in this group may have presented bronchitic signs which were not observed, and so should be placed in Group B 1. Some of them, however, were examined daily throughout their illness from the onset, and no signs were ever found; thus the infection may descend no lower than the trachea.

In this group bacteriological examination reveals a flora remarkable only for the absence of the organisms usually associated with pneumonia, and the blood shows an absence of leucocytosis except during convalescence in some cases.

In Group B the picture seems to be a gradually increasing involvement of the bronchial tree. The sequence of suppressed breathing followed by return of the breath-sounds with râles, which was observed in Group B 1, merits further attention. When it was first observed it was thought that the probable mechanism was blockage of a small bronchus or bronchiole with secretion, giving rise to the suppression of breath-sounds, followed by aspiration of the secretion into the bronchioles, giving rise to the return of the breath-sounds with moist râles. On this theory it was expected that some lobular atelectasis would be observable, but radiological examination in all these cases, as noted above, failed to show any evidence of this. Moreover the constancy of these areas at any one examination, and the fact that coughing or deep respiration did not influence them, is evidence against this theory. I think, therefore, that this sequence of physical signs is more likely to be due initially to partial obstruction of a small bronchus by inflammatory swelling of the mucosa, giving rise to the stage of suppression of the breath-sounds. Should the inflammation subside and descend no further, the area of suppression disappears without giving rise to subsequent râles; should the infection descend the bronchial tree to the finer ramifications, subsidence of the oedema of the stage of suppression gives rise to persistent râles due to this bronchiolitis or alveolitis.

Group B 2, the cases which showed clinical evidence of involvement of lung bases in the form of impairment of percussion-note and weak or absent breath-sounds, without radiological evidence of consolidation, could well be accounted for by a further descent of this inflammatory process, giving rise to an inflammatory oedema short of actual consolidation.

In this group, again, no characteristic bacterial flora can be recognized; pneumococci have appeared but are not prominent, and are usually of Group IV. The significance of the prominence of *N. catarrhalis* in the flora of the group is difficult to assess. It seems reasonable to suppose that it may modify the course of the bronchitis and bronchiolitis in the role of a secondary invader. The leucocyte count shows no change from that of Group A, except in the more severe cases, where a rather earlier leucocytosis may be observed; possibly in these, secondary infection is responsible. On the whole, however, it seems likely that the influenzal infection alone can descend to the bronchioles, and that bacteria are acting as relatively unimportant secondary invaders in Group B.

Group C seems to be most easily explicable as a combination of the lesions described in any of the preceding groups with a pneumonic consolidation. Thus, Group C 1 could be regarded as Group B 2 with the addition of patchy basal consolidation; Group C 2 as this condition plus an actual lobar consolidation; Group C 3 seems to be a combination of Group B 1 with a partial lobar consolidation; while Group C 4 seems

to be a combination of Group B 1, or even Group A with a lobar consolidation.

When the results of sputum culture are compared with this conception, we find that in Group C pneumococci have become the most prominent organisms. On analysing further, it is found that in half the cases of sub-Groups C 1 and C 2, pneumococci or staphylococci are the predominant pathogens, while in Groups C 3 and C 4 which clinically approached most nearly to the usual type of lobar pneumonia, pneumococci predominated in every case.

In the single case of fulminating pneumonia also, *Staphylococcus aureus* was found in enormous numbers in the lung at autopsy.

These observations make it probable that bacterial agents were concerned in the production of the consolidations observed in this group. But clinically these pneumonias were quite unlike the usual type of pneumococcal pneumonia, as indicated above. It therefore seems that we are dealing with the resultant in the lung-tissue of both bacterial and the original influenzal infections. This idea receives some support from the manner in which the physical signs of the influenzal lobar consolidations differed from those of simple pneumococcal lobar pneumonia: it is easy to conceive of the grafting of a bacterial lobar consolidation on to the oedematous base of Group B 2 causing the extreme dullness with weakness of breath-sounds which characterized the consolidations of Group C. Another clinical observation which supports this view is that in over half the cases the onset of 'pneumonic' symptoms could be dated by the onset of fresh symptoms or recrudescence of previous symptoms.

Considering the question from the point of view of the blood changes, the occurrence of leucocytosis early in some cases of Group C, as opposed to the normal counts found in other groups at a corresponding time in the course of the disease might well be associated with an added bacterial invasion of the lung.

As a tentative hypothesis, it may be suggested that the initial virus disease is a descending infection of the respiratory tract which may stop short at any level. It may extend as far as a bronchiolitis, when a clinical picture approximating to that of Group B 2 will be produced. Bacterial invasion will modify the picture in various ways. It may alter the type of and prolong an influenzal bronchitis. A low-grade bacterial infection super-added to the 'oedematous base' picture may give rise to a patchy bronchopneumonia as in Group C 1. A more virulent bacterial infection proceeding to lobar consolidation in a similar case will produce the picture of Group C 2. If an influenza extending no further than a large tube bronchitis is complicated by a bacterial infection proceeding to lobar consolidation, the picture will differ less from that usual with such consolidations, and a case of Groups C 3 or C 4 will result. If a combination of extensive virus damage with a simultaneous virulent bacterial infection occurs, an acute fulminating pneumonia may be produced.

Comparison of the Lung Changes of this Series with those recorded in Pandemic Times

In comparing the clinical features of the present series with those of pandemics, the fact that I have not observed a pandemic places me at a disadvantage. However, on consulting the literature of pandemic times, certain resemblances between the lung changes recorded and those of the present series became evident. It may be mentioned that the description of the lung changes given above was outlined before any special study of the previous literature had been made: it was frequently noted that forms of words had been used in the notes of the present series almost identical with those used by writers describing the clinical features of lung changes in pandemics. In the following comparison, it has been practicable to give only a few references out of the enormous mass of literature.

Group B. The occurrence of pulmonary physical signs in cases of influenza running a brief normal course and comparable with those noted in the less severe cases of Group B 1 was recorded by Bloomfield and Harrop (1919). In 19 patients out of about 300 they found 'localized patches of fine crackling râles, with some impurity of breath-sounds. These signs usually appeared at the height of the disease and persisted for a few days to several weeks. . . . In no case was there bloody sputum, respiratory symptoms or any unusual rise of temperature. The normal course of the disease seemed unaltered. X-rays made in several of these cases showed no localized shadow'.

The great variability and variety of the added sounds in 'bronchitic' cases was a constant finding (Leichtenstern (1905), French (1920), Russell (1919)). Areas of diminution of the breath-sounds were described (French (1920), Russell (1919), Martin (1919)). The frequent occurrence of rhonchi anteriorly with râles at the base was noted (French (1920), Russell (1919)).

Group C. The difficulty of classification of the consolidations was commonly noted, but it appears clear that the proportion of consolidations of lobar extent observed in different localities varied considerably. This could probably be correlated with the prevalent type of bacterial infection (see below). When these local differences have been discounted there remain certain common features which distinguished an influenzal from a non-influenzal consolidation.

The time of development of symptoms and signs of pneumonia was generally in substantial agreement with that noted in the present series. Thus French (1920) notes that in most cases the patient had been ill for a day or two with ordinary simple influenza when the 'pneumonic' complication developed; in some cases there was no 'influenza' period at all; in others the pulmonary complications were later in their development, setting in after the patient had had no symptoms other than those of ordinary influenza for nearly a week, or even coming on when the patient was apparently quite convalescent.

The general aspect of the patients in the present series was one of their most striking features. Similar observations were recorded by numerous workers in pandemic times. Thus French (1920) noted the relative absence of respiratory distress with marked tachypnoea and cyanosis; the pulse often remaining of good volume right up to the end. Martin (1919) noted that apathy was a constant feature of the picture, and that cyanosis often preceded dyspnoea. Chickering and Park (1919) noted that 'these patients rarely have the painful and laboured breathing seen in pneumococcus infections'.

The frequently atypical nature and incompleteness of the signs of consolidation over pneumonic areas was noted by Leichtenstern (1905); the first indications of pneumonia were small areas of 'relative dullness, fine crepitant râles, sub-bronchial breathing and weak bronchophony'; the pneumonic areas throughout the whole course did not show pure bronchial breathing but fine râles with relative dullness and bronchophony, and these areas were frequently bilateral. Later he stated that lobar influenzal pneumonia might run a protracted course, so that after defervescence, complete dullness and bronchial breath-sounds might persist without râles for a week or longer. In such cases he found difficulty in deciding whether fluid were present until needling had shown its absence. He also mentioned cases showing the opposite tendency, in which fully developed pneumonic symptoms and signs resolved unexpectedly in from one to three days (cf. Case 11). French (1920) observed that definite lobar signs were found in only a few cases. He noted the occurrence of patches of consonating râles without bronchial breathing or pectoriloquy, which might persist, spread, or retrogress; later they might be accompanied by dullness, and later still with bronchial breathing. He remarked on the fact that areas of bronchial breathing might be transient, suggesting a temporary collapse. He also observed cases having basal dullness with absent breath-sounds and voice conduction. The extensiveness of the signs bore no relation to the degree of illness or to the cyanosis. Chickering and Park (1919) observed a 'very atypical type of pneumonic involvement'. They found most commonly diminished resonance to percussion, weak breath-sounds, and many fine and coarse râles at both lower lobes, pure consolidation signs being rare and late.

The irregular nature of the pyrexia, even in definitely lobar consolidations, was also commonly noted. French (1920) noted the extreme variability of the pyrexia, and stated that there was nothing in the temperature charts to indicate whether the patient was doing well or badly. Crisis was very rare indeed. Bock and Stoddard (1919) observed great diurnal variations in the temperatures of their broncho-pneumonic cases, but a higher temperature, 102° to 105° in the cases of lobar pneumonia. Maude (1918) noted that hardly any of the cases of lobar consolidation ended by crisis, and in many the lysis was very irregular; and also that when purulent expectoration was established, a swinging type of temperature occurred.

On the other hand, Russell (1919) observed crisis in cases with lobar consolidation, though irregular types of pyrexia were seen in other cases.

With regard to the sputum, one great difference between that observed in the present series and that described in the pandemics is the rarity of haemoptysis in the present series. The early 'pink frothy mucus' described by Horder (1918), Leichtenstern (1905) and others was not seen.

Apart from this, the general character of the sputa in the present series is very similar to that described in pandemics. In particular, the 'discrete pellets' which have been described above were mentioned in many accounts of pandemics. Thus French (1920) referred to 'pellets or dollops of muco-pus, the individual expectorations remaining separated from one another in the disinfectant in the sputum pot'. He describes its quality as sometimes glairy, sometimes pure pus. Russell (1919) spoke of 'small tough whitish lumps'. Leichtenstern (1905) described an almost purulent, nummular, occasionally globular sputum found early at the height of the influenza attack. Martin (1919) stated that the sputum appeared first as small lumps of muco-pus, somewhat viscid, and later becoming nummular. Bock and Stoddart (1919) described the sputum of broncho-pneumonic cases as 'characteristic of influenza, pale green, nummular'. Most observers agreed in describing the sputum of generalized bronchitic cases as profuse and purulent, but noted that other cases might expectorate very little (see especially French (1920)). The striking variations in colour of the sputum noted in some cases by Horder (1918), French (1920), and others were represented in the present series by one case in which the sputum was a rather bright orange colour.

The Relation between Pandemic and Inter-pandemic Influenza

It may reasonably be inferred from this comparison that the clinical difference between the pandemic and the inter-pandemic outbreaks of influenza is one of degree rather than of essential nature. The incidence of serious lung involvement in pandemics is clearly very much higher: but when such involvement does occur in minor epidemics, it assumes a form clinically similar to that of pandemics. The mortality among the patients who actually showed evidence of consolidation in the present series was 37 per cent.; French (1920) estimated the mortality of 'pneumonic' cases in autumn 1918 as 40 per cent.; Opie, Freeman, Blake, Small, and Rivers (1919) found a mortality of 31 per cent. among 1,499 pneumonic cases; Chickering and Park (1919) 27.5 per cent. among 1,400; Brem, Bolling, and Casper (1918) 36 per cent.

A statistical survey by Collins (1931) suggested that the case-mortality of pneumonic cases in the 1928-1929 epidemic in U.S.A. was very similar to that in the pandemic of 1918-19; but the case-incidence was much lower, and the age-incidence was different, the young adult peak of 1918-19 being absent in 1928-29. Such obvious differences in epidemiological character

have been much stressed as indicating an essential difference in etiology between the two groups; but similar variations in the age-incidence and fatality of other infectious diseases are well known, though usually more gradual and therefore less dramatic.

Two recent observations may have some bearing on this point. Andrewes and Smith (1937) have reported a spontaneous sudden change in the infective titre of their W.S. strain of human influenza virus after repeated passage through mice.

Shope (1936) discussing the relation between the viruses of swine influenza and of human influenza, advances some evidence for the suggestion that his swine influenza virus is a remnant of the 1918 human epidemic; the present human virus being a closely related but distinct strain. He has shown that typical swine influenza is produced only by a simultaneous infection with the virus and *H. influenzae suis*; the virus alone producing a much milder disease. He suggests that an essential difference between the two viruses is the better developed ability of the swine influenza virus (which he regards as possibly 1918 human virus) to act synergistically with bacteria.

Interesting as such hypotheses are, it appears likely that the exact relation between past pandemics and present epidemics will remain a subject for speculation: in any future pandemic, the question of the relation of its virus to the present strains will doubtless be answered by laboratory test.

The Rôle of Bacteria in the Lung Lesions in Pandemic Times

Many workers, even before the demonstration of the influenza virus, expressed the opinion that the bacteria commonly found in association with the lung changes of influenza were acting in combination with or secondarily to a then unknown agent.

Thus MacCallum (1921), who believed that influenza was produced by 'some infective agent which differs from any of those which we have definitely recognized in that we cannot see it, nor stain it, nor infect animals with it', wrote:

'Those who had opportunities of observing the disease in several widely separated places were readily convinced that although the influenza was uniform and constant in every place, the type of bacterial infection producing the pneumonia differed with the locality and depended on the local prevalence . . . of some virulent organisms. . . . It became quite clear that the bacterial invasion was essentially a secondary phenomenon the result of the great lowering of the resistance of these individuals by the primary disease influenza which laid them open to infections of the intensest character with almost any organisms they happened to inhale. This infection assumed the most destructive violence because the evident lowering of the resistance of the tissues left them to react merely like an inert culture medium in which bacteria could grow in unheard of quantities.'

Substantially similar views were expressed by Goodpasture (1919),

Cummins (1920), Jordan (1927), Opie (1928), and others; influenzal lung lesions being attributed to the combined action of an unknown primary agent and a bacterial infection. The evidence consisted of several sets of observations.

1. Pathogenic bacteria, it was stated, were always to be found in the lungs of patients dying of influenzal pneumonia. Search of the literature has revealed records of only two cases in which organisms were neither cultured from the lungs nor seen in sections: these were recorded by Goodpasture (1919 *b*). Several other observers reported cases in which culture from the lungs was sterile; but these few observations do not invalidate the general statement that pathogenic bacteria were constantly present in the consolidated lungs.

2. Both the type of lung lesion and the prevalent bacterial flora varied considerably in different localities. Wolbach (1919) wrote: 'In comparing notes with other pathologists, one is struck by the differences in gross appearance of lungs from different localities. The same is true in regard to the bacteriology'. There was much evidence that variations in the clinical picture could be correlated with variations in bacterial flora. For example, Stone and Swift (1919) found lobar consolidations in 76.2 per cent. of their pneumonic cases; in their series, pneumococci were very commonly found. Chickering and Park (1919) dealing with a locality where *Staphylococcus aureus* was found in the lung in 153 out of 312 autopsies, found that pure consolidation signs were rare and late. Empyema was noted to be of common occurrence in outbreaks associated with haemolytic streptococci (Goodpasture (1919 *a*); Manson (1919); Opie (1928)), but was rare in association with other organisms. A bronchitis with profuse purulent expectoration was usually associated with Pfeiffer's bacillus (Opie et al. (1919); Abrahams, Hallows and French (1919)); and resembled the 'purulent bronchitis' associated with this organism observed in France before the pandemic (Abrahams, Hallows, Eyre, and French (1917); Hammond, Rolland, and Shore (1917)). Haemorrhagic oedematous pneumonia was commonly associated with haemolytic streptococci (Tytler, Janes, and Dobbin (1919); Fildes, Baker, and Thompson (1918); Lucksch (1928)); it also occurred in association with staphylococci (Chickering and Park (1919)). In the 1928 epidemic Burgess and Gromly observed three fatal cases of 'fulminating' pneumonia associated with *Staphylococcus aureus*, presenting the appearance of 'the typical wet lung of the 1918 epidemic'; these cases seem to have been remarkably similar to Case 13 of the present series.

Logan (1921) examined sputa or pharyngeal swabs during the pandemic. In 'pure influenza'—i.e. cases without pulmonary involvement—he found pneumococci in 13.6 per cent. and haemolytic streptococci in none; in those with pulmonary involvement, he found pneumococci in 78.1 per cent. and haemolytic streptococci in 28 per cent. Moreover, in 34 instances the pneumococcus found was typed; type I, II, or III were found in eight cases, all of which had or developed consolidation.

Ward epidemics of secondary invasion of influenzal cases of various organisms, notably haemolytic streptococci, were recorded (Opie et al. (1919)).

3. Many pathologists regarded certain pulmonary lesions as typical of influenza; some described also characteristic lesions constantly produced by particular types of secondary bacterial infection. The chief lesions regarded as typically influenzal were severe injury to bronchi and bronchioli with desquamation of epithelium and even necrosis; exudation into the interstitial, peribronchial and perivascular tissues; the formation of a layer of hyaline material on the inner surface of dilated alveolar ducts and infundibula; and focal necrosis of alveolar walls with hyaline thrombosis of capillaries and intra-alveolar haemorrhage (Wolbach (1919); Goodpasture (1919); MacCallum (1921); Winternitz, Wason, and McNamara (1920); Opie (1928); Lucksch (1928)). In addition to these changes, MacCallum described separately the features of the influenzal pneumonias associated with pneumococci, streptococci, and Pfeiffer's bacillus, and a group of 'fresh pneumonia' which might be associated with various organisms. Opie (1928) while concluding that influenzal broncho-pneumonia may be associated with a great variety of bacteria, recognized types of pneumonia caused by haemolytic streptococci and by staphylococci and noted the greater frequency of pneumococci in cases with lobar consolidations. He also described typical changes in lungs of influenzal cases already invaded by pneumococci after subsequent invasion by streptococci. Goodpasture and Burnett (1919) described characteristic changes in the pathology of the lungs produced by pneumococci and streptococci. On the other hand, Winternitz, Wason, and McNamara (1920) found no evidence of a relationship between the type of bacteria and the distribution or nature of the pneumonia.

4. The similarity of the lung lesions to those initiated by the inhalation of poisonous gases was noted (Winternitz, Wason, and McNamara (1920); French (1920); Wilson and Steer (1919); Underhill and Ringer (1920)). In these gas cases the primary lesion was a chemical necrotizing inflammation of the respiratory tract; secondary invasion of the lung by various organisms gave rise to a pathological picture suggestively similar to that of influenzal pneumonia. This analogy was particularly drawn by Winternitz et al., who concluded that there was 'no reason why we should not consider that the unknown etiological agent in influenza produces a similar injury to, or even destruction of, the protective mechanism of the respiratory tract. Similarly, gas and influenza damage the pulmonary parenchyma itself, so that the bacteria of the air and of the mouth which find their way into the damaged lung initiate processes and produce complications which may not be distinguished.'

Pure Virus Pneumonia

It appears clear, from the foregoing, that bacteria have played an important part in outbreaks of influenza, whether pandemic or otherwise, in determining the severity and nature of the pulmonary lesions. Granting

the virus etiology of influenza, a complementary and crucial point is the possible extent and severity of a pure virus pneumonia in man. The two cases of fatal influenza in the consolidated lungs of which bacteria could not be demonstrated either by culture or direct microscopical examination, recorded by Goodpasture (1919 b), are important in this respect. They appeared clinically to run a similar course to other pneumonias observed at this time, except that one had apparently occurred in the course of a recurrent attack of influenza; they were not notably acute or rapid in their course, and the gross and microscopic pathology was similar to that observed in many other cases.

In mice and ferrets, virus pneumonias have been produced by the human influenza virus, and may be fatal though free from bacteria. Complete reports on the histology of these consolidations are not yet available; from a preliminary report (Andrewes, Laidlaw, and Smith (1934)) it appears that the chief features are that the bronchi contain desquamated epithelial cells and leucocytes with pyknotic nuclei; there is some oedema and leucocytic infiltration round bronchioles and blood-vessels, and the alveoli contain mainly non-fibrinous fluid and red and white blood-cells. The similarity between these and the features regarded as distinctively influenzal in the picture of the human disease is evident. In a further paper (Laidlaw, Andrews, Smith, and Dunkin (1935)), some unusual features in the histology during the stage of resolution were noted; in areas which appeared to have been the site of severe damage, a superficial resemblance to a secreting gland was presented, the original air-sacs being lined with cubical or columnar epithelium; up to one month from infection, cubical epithelium might be seen in half a lobe. Very similar features were described by McNamara (1919) and Winternitz et al. (1920) in the more chronic fatal human cases. The former described 'actively dividing young epithelial cells. . . The histological picture is exactly like that of a carcinoma.'

Bacteria and Virus in the Lung Lesions

The conclusions that may reasonably be drawn from a correlation of these recent observations on experimental influenzal pneumonia in animals and the older clinical and pathological observations on the human disease agree well with the tentative interpretation of the clinical picture of the present series suggested above.

1. A pure influenza virus infection of the human lung can probably descend to any level of the respiratory tract. If it proceeds to an actual alveolitis, a clinical picture of oedematous lung bases with possibly some actual patchy consolidation is produced.

2. Such virus pneumonias are very rarely, if ever, fatal before invasion of the lung by bacteria, usually pneumococci, haemolytic streptococci, Pfeiffer's bacillus or staphylococci has occurred.

3. In determining the severity and the extent of the consolidation, bacteria

play an important part. Any combination of extent of virus damage and virulence of bacterial invasion can occur. Thus a case in which an influenza descending no lower than the bronchi has paved the way for an invasion by virulent pneumococci will present a clinical picture differing little from that of ordinary lobar pneumonia; while a case in which the influenza virus infection is predominant and bacterial invasion late and of relatively little importance will present a picture farthest removed from that of an ordinary bacterial pneumonia. It is probable that the rapidly fatal fulminating cases are the result of an extensive virus infection plus early invasion by virulent bacteria.

Summary

1. A clinical study of the lung changes in 58 cases of influenza admitted to Hammersmith Hospital, London, in December 1936 and January 1937 is presented. From four of these the influenza virus was isolated.

2. Twenty-two cases presented abnormal pulmonary physical signs without radiological evidence of consolidation. In the less severe cases of this group, areas of 'suppressed' breath-sounds at the bases were the most distinctive physical signs. The more severe ones presented a clinical picture of oedematous lung bases, and their general aspect resembled that of patients with actual consolidation.

3. Nineteen had actual consolidation. Of these, seven died. The characteristics of the signs of consolidation were extreme dullness to percussion, weak tubular or bronchial breath-sounds, and aegophony.

4. Bacteriological studies of the sputa showed that the bacterial flora of the series as a whole was no different from that of the non-influenzal sputa examined during the period of the epidemic. Analysis of the results according to the clinical grouping showed significant differences between the bacterial type-distributions in the various groups: pneumococci, which were absent from the sputa of the group without evidence of pulmonary involvement, predominated in the group of those with consolidation.

5. One case of fulminating 'influenzal' pneumonia, fatal on the third day, is described. In the lung both *Staphylococcus aureus*, in enormous numbers, and the virus were demonstrated.

6. A comparison between this series and the descriptions of the disease in pandemic times is made. It is concluded that the difference between them is one of degree rather than kind.

7. Observations of workers in the 1918 pandemic on the role of bacteria in the lung changes in influenza are reviewed.

8. It is concluded that the influenza virus can produce severe changes in the lung in man which facilitate invasion by bacteria. The course of the disease depends upon the extent and virulence both of the virus and of the bacterial infection; the extraordinary variability of the clinical picture is due to the numerous possible combinations of these factors.

Acknowledgements

I wish to express my thanks to Professor F. R. Fraser for giving facilities for the clinical study and for much help and criticism; to Dr. Janet Vaughan, Dr. A. A. Miles, Dr. F. D. Johnstone, and Dr. J. Gray for allowing me to incorporate so much of their pathological work in this paper; and to Dr. C. H. Andrewes for permission to use the results of the virus tests. I am also indebted to Sir Frederick Menzies, Chief Medical Officer, London County Council, for permission to publish the case-records.

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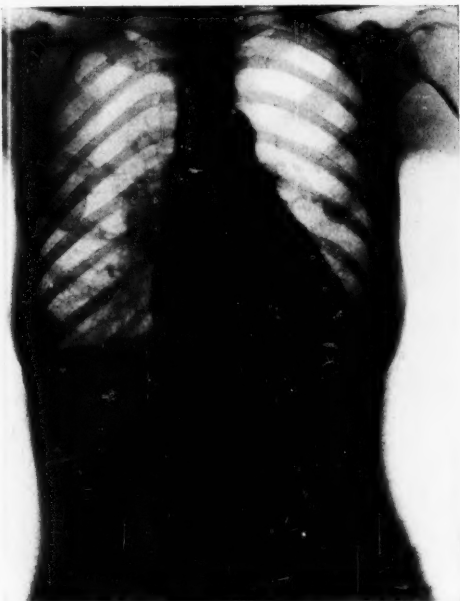


FIG. 1. Case 3. Jan. 2



FIG. 2. Case 4. Jan. 11

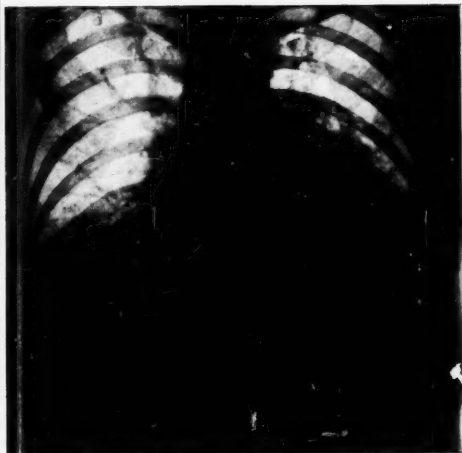


FIG. 3. Case 5. Jan. 2

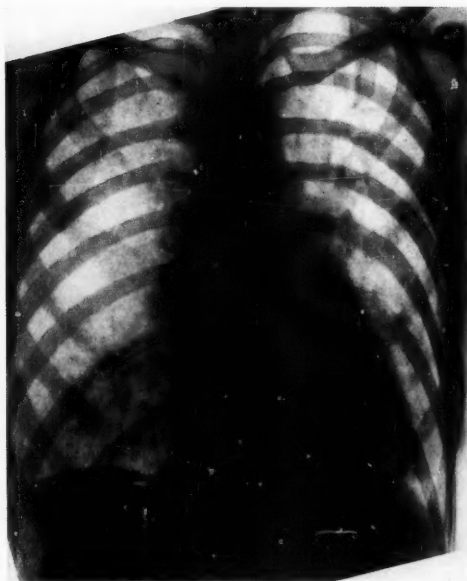


FIG. 4. Case 6. Jan. 7

In Figs. 1 and 2 (Group B 2), note the absence of evidence of consolidation.

In Figs. 3 and 4 (Group C 1), note the patchy coarse mottling at the bases, suggestive of broncho-pneumonia.



FIG. 5. Case 7. Jan. 4

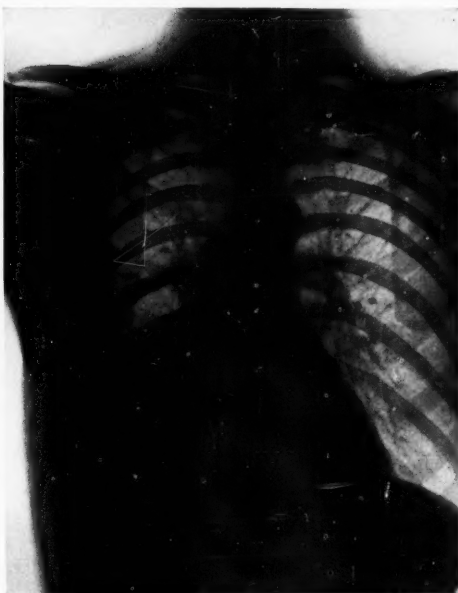


FIG. 6. Case 7. Feb. 12

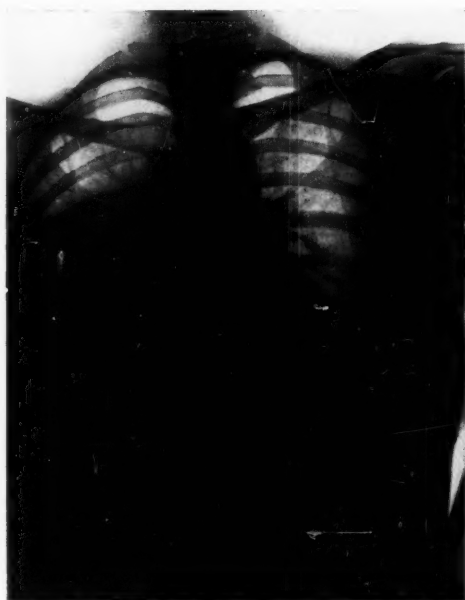


FIG. 7. Case 8. Jan. 2

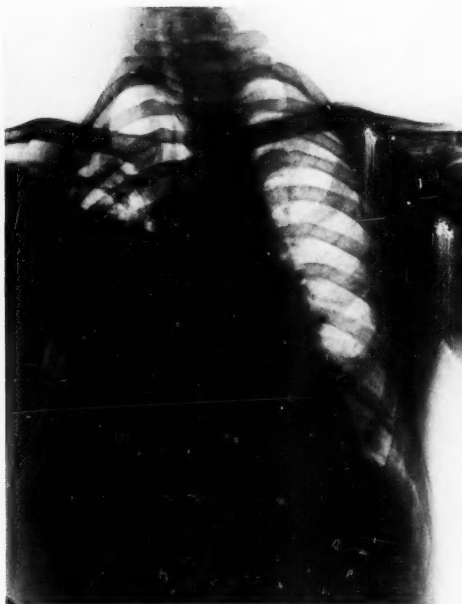


FIG. 8. Case 9. Jan. 12

In these plates (Group C 2), note the extreme density of the consolidated areas, and the slow resolution in Case 7 (Figs. 5 and 6).

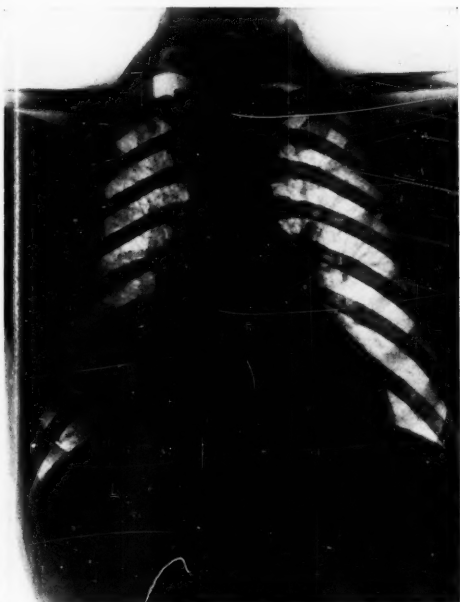


FIG. 9. Case 10. Jan. 15

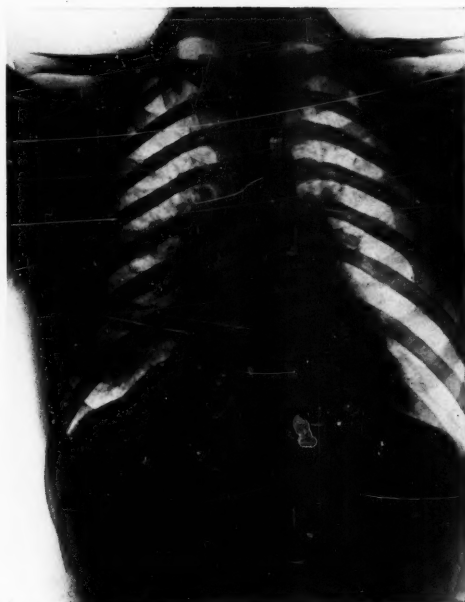


FIG. 10. Case 10. Jan. 26

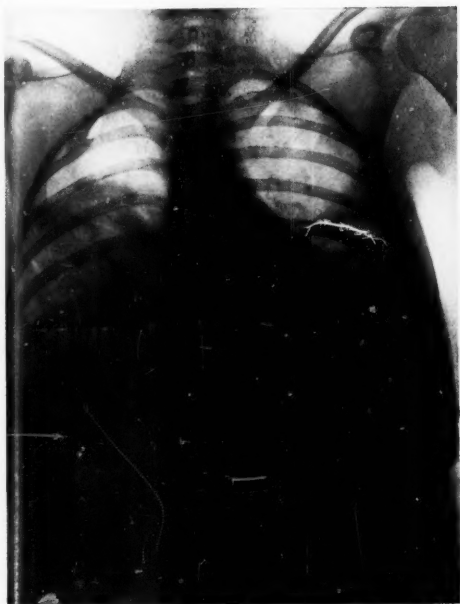


FIG. 11. Case 11. Jan. 7

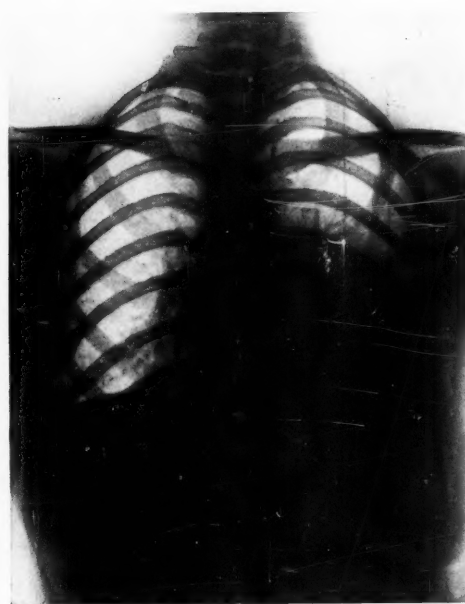
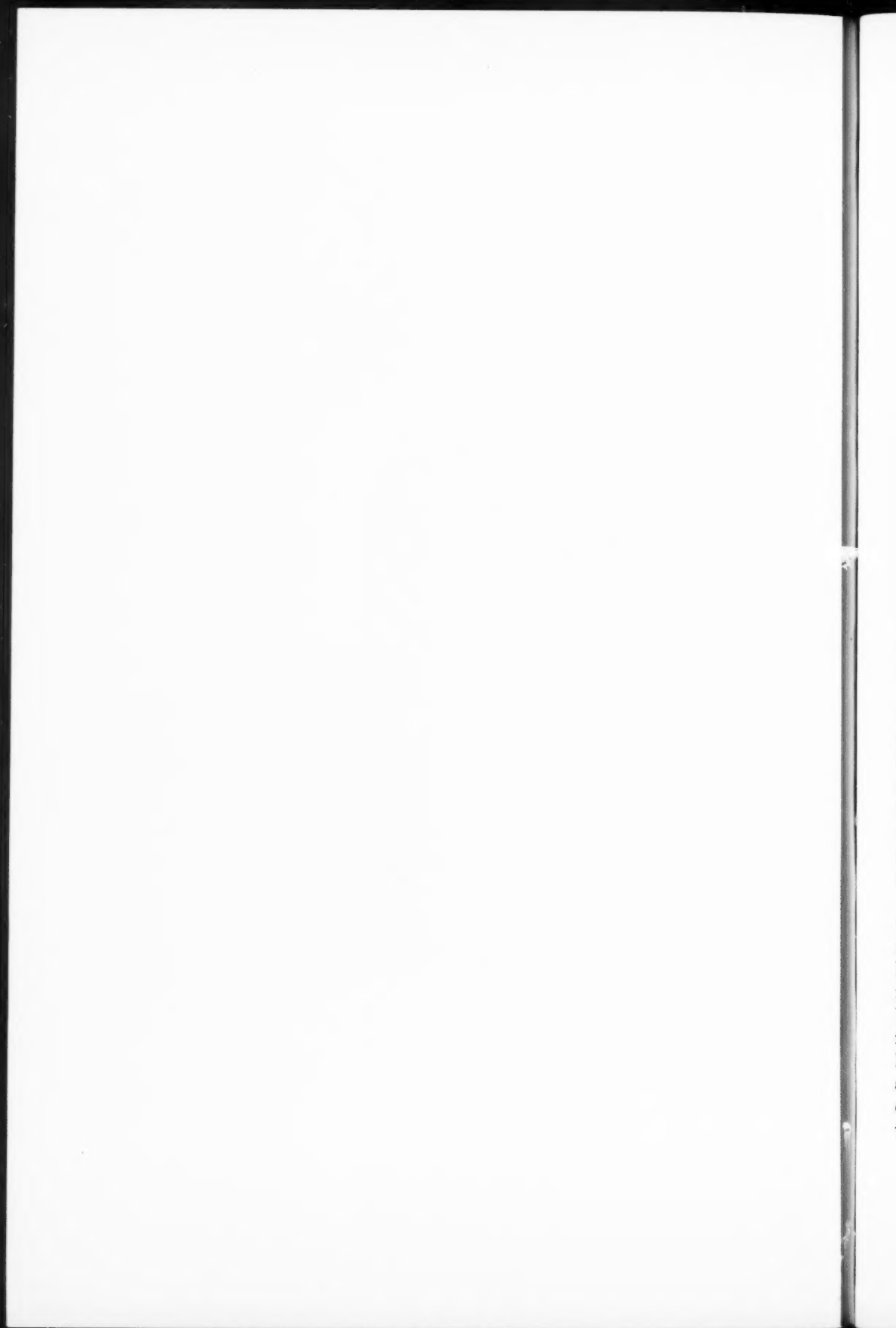


FIG. 12. Case 12. Jan. 11

In these plates (Groups C 3 and C 4), note the dense opacity of the consolidations, and the speedy resolution in Case 10 (Figs. 9 and 10).



PLASMA LIPIDS IN THE DIAGNOSIS OF MILD
HYPOTHYROIDISM¹

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THE secretion of the thyroid gland has been demonstrated to exert a controlling influence over the concentration of lipids in the blood plasma of man (3, 6, 7). Hyperthyroidism is accompanied by a statistically significant lipopenia (7) and from previous studies it appeared that the converse phenomenon, a lipaemia, appeared in hypothyroidism (6). In the present investigation an attempt was made to evaluate the significance of plasma lipid estimations in cases in which a tentative and provisional diagnosis of mild hypothyroidism was made. The diagnosis of an obvious case of myxoedema requires no confirmatory data from the laboratory. There are, however, many patients who present one or two symptoms or signs suggesting hypoactivity of the thyroid gland but in whom a positive diagnosis cannot immediately be made.

In the present series are included 35 such cases. When first examined these patients were noted to exhibit one or more of the following: a slight gain in weight, mental or physical sluggishness, menstrual disturbances, coldness or numbness of the extremities, vague pains in the joints, dry or rough skin or nails, and in practically all instances a subnormal basal metabolic rate. One or more complete, differential lipid analyses of blood plasma were made on each patient, using the oxidative micro-methods of Bloor as modified by Boyd (2). The lipid analysis was done before instigating treatment with thyroid.

After sufficient time had elapsed to permit of a proper adjudication of the value of treatment, the cases were divided into those whose symptoms were not relieved by thyroid and those whose symptoms were relieved by thyroid. In the second group, relief of symptoms was usually obtained within two to four weeks during which interval the optimum dose had been established. Where relief was not obtained, a thorough trial lasting in some instances from three to six months was allowed before the therapy was discontinued. By comparing the lipid values in each of these groups, it was possible to ascertain whether or not the estimation of plasma lipids was of value in distinguishing cases of true, mild hypothyroidism (which would respond to thyroid) from cases whose symptoms simulated hypothyroidism but in

¹ Received July 10, 1937.

which such was not the correct diagnosis (as subsequently shown by failure to respond to thyroid).

Plasma lipid values in suspected cases of mild hypothyroidism which did not respond to medication with thyroid have been depicted in Table I. There were 19 cases in this group, and of these the basal metabolic rate was determined in 15 cases. In only one instance was the basal metabolic rate

TABLE I

The Lipid Content of Blood Plasma in Cases of Suspected Mild Hypothyroidism which were subsequently not improved by Thyroid. The Results are expressed in mg. per 100 c.c. of Plasma.

Case.	Basal metabolic rate.	Total lipid.	Composition of total lipid.					
			Neutral fat.	Total fatty acids.	Cholesterol.			Phospho- lipid.
					Total.	Ester.	Free.	
1	-24	433	83	250	124	93	31	164
2	-12	559	101	236	150	109	41	235
3	-30	460	92	260	141	97	44	162
4	-20	513	183	320	140	90	50	130
5	-20	518	220	347	114	69	45	138
6	-10	576	96	313	192	134	58	198
7	-20	465	76	264	135	99	36	188
8	-15	420	105	241	134	89	45	121
9	+18	430	125	250	141	99	42	98
10	-21	592	168	366	145	86	59	221
11	0	577	163	344	169	115	54	168
12	0	581	164	341	181	126	55	152
13	...	503	122	281	175	124	51	123
14	-14	572	154	323	197	133	64	132
15	-32	508	171	319	135	102	33	134
16	...	648	298	437	149	90	59	141
17	...	465	225	307	115	45	70	95
18	-11	599	195	363	172	105	67	162
19	...	509	143	317	119	75	44	197
Mean	-14	522	152	320	149	99	50	156
Standard deviation	12	62	56	52	24	21	11	39
Expected range of 2/3 of cases	-2 to -26	460-584	96-208	268-372	125-173	78-120	39-61	117-195

above the average normal and the lowest reading obtained was 32 per cent. While a number of values for the basal metabolic rate was within the normal range, it should be noted that the provisional diagnosis of mild hypothyroidism was not based solely on the basal metabolic rate. In fact the diagnosis was made in most instances before the rate had been determined. The average basal rate of the 15 cases in which it was determined was 14 per cent. and the standard deviation of the mean rate (calculated by a formula previously used (2)) was 12.

The values for plasma lipids presented in Table I are not significantly different from those of normal human adults. In fact the means and standard deviations of this group of suspected but not true cases of hypothyroidism are practically identical with those reported by one of us (4) for normal persons. For example, the expected range of total lipid in two thirds of cases calcu-

PLASMA LIPIDS IN DIAGNOSIS OF MILD HYPOTHYROIDISM 469

lated from Table I was 460 to 584 mg. per 100 c.c. of plasma and the similar range of normal values (4) was 456 to 604 mg. per 100 c.c. Corresponding comparative values for neutral fat were 96 to 208 as against 82 to 202; for phospholipid, 117 to 195 as against 137 to 193; for free cholesterol, 39 to 61 as against 38 to 54. The conclusion may be made that cases of suspected mild hypothyroidism which subsequently will not respond to thyroid are

TABLE II

The Lipid Content of Blood Plasma in Cases of Suspected Mild Hypothyroidism which subsequently improved under Thyroid. The Results are expressed in mg. per 100 c.c. of Blood Plasma.

Case.	Basal metabolic rate.	Total lipid.	Composition of total lipid.					
			Neutral fat.	Total fatty acids.	Cholesterol.			Phospho-lipid.
					Total.	Ester.	Free.	
20	...	933	272	567	257	178	79	285
21	-10	793	118	382	224	159	65	245
22	-33	769	216	458	225	154	71	225
23	...	690	141	371	242	142	100	212
24	-15	715	237	445	195	142	53	188
25	-10	639	163	367	207	147	60	170
26	+8	635	204	393	176	131	45	167
27	-8	638	160	360	219	160	59	152
28	...	660	283	430	178	126	52	115
29	0	667	122	379	210	149	61	245
30	+15	685	295	463	148	99	49	176
31	-10	726	252	463	180	124	56	211
32	0	633	104	330	231	146	85	200
33	-29	857	177	493	260	200	60	286
34	...	855	397	572	200	105	95	188
35	-20	629	184	370	194	126	68	167
Mean	-9	727	208	427	209	143	66	202
Standard deviation	13	91	74	69	30	24	15	46
Expected range of 2/3 cases	+4 to -22	636-818	134-282	358-496	179-239	119-167	51-81	156-248

characterized by normal values for plasma lipids. There are occasional exceptions to this in Table I, but in general it is true.

On the other hand, the group of 16 cases provisionally diagnosed as mild hypothyroidism which subsequently did respond to thyroid, showed a significant elevation of values for plasma lipids. Table II presents the data obtained from this group. Curiously, the average basal metabolic rate of this group was not as low as that of the preceding group. In these cases, the estimation of the basal metabolic rate appeared less reliable than the estimation of plasma lipids as an aid in arriving at a diagnosis of true, mild hypothyroidism.

All of the cases of true, mild hypothyroidism shown in Table II were found to exhibit a definite lipaemia. In most instances the lipaemia was slight, which was to be expected since the degree of hypothyroidism was slight. In every instance the total lipid of plasma was higher than the maximum value calculated for the expected range of two thirds of normal subjects, which is 604 mg. per cent. (4). In other words, all of the values

for total lipid in Table II were higher than those which one may expect to encounter in five out of six cases of normal adults at random sampling.

All of the component lipids of plasma in Table II except neutral fat showed a similar or greater significant difference from normal and from the cases presented in Table I. The most significant differences were encountered in comparing the values of total fatty acids, total cholesterol and ester cholesterol. There was slight overlapping in the figures for phospholipid and free cholesterol. There was considerable overlapping in the values for neutral fat, so much so in fact that there was no significant difference between the neutral fat values in the two groups or between the group in Table II and normal values.

The latter fact is interesting since Bloor (1) has emphasized that in a lipaemia the neutral fat values are usually elevated to the greatest extent. This is true in the lipaemias of diabetes, pregnancy, nephritis, and nephrosis. In mild hypothyroidism it has been shown that those lipids increased the most are cholesterol and phospholipid; lipids which are sometimes referred to as lipoids. The condition might thus be termed the lipoidaemia of mild hypothyroidism to distinguish it from a true lipaemia. A similar lipoidaemia has been found to follow the completion of abortion in women (5).

The results constitute a further justification of the distinction made between the two groups of cases in the present series. They indicate that the group which responded to thyroid possessed a metabolic disturbance not evidenced by the other group. In conjunction with previous work in this field, the results demonstrate that only about one half of patients presenting symptoms which suggest a provisional diagnosis of mild hypothyroidism are actually suffering from a deficiency of thyroid function. The estimation of plasma lipids has been shown to be a convenient and satisfactory way in which to differentiate these cases of true mild hypothyroidism from cases simulating hypothyroidism.

There are advantages to be gained from a complete, differential lipid analysis rather than from what is more commonly done, the estimation of total cholesterol alone. The estimation of all of the lipids provides a much more complete picture of the change in metabolism. Changes in the concentration of total fatty acids, total lipid, phospholipid and other fractions bear just as close a relation to thyroid deficiency as changes in total cholesterol. The complete analysis also provides a check on the analytical method; there is less chance of analytical error appearing in all of a series of values on one sample of blood than in one single determination. A scrutiny of the individual values listed in the accompanying tables will reveal instances in which the wrong conclusion would have been made had reliance been placed on certain of the single values.

Conclusion

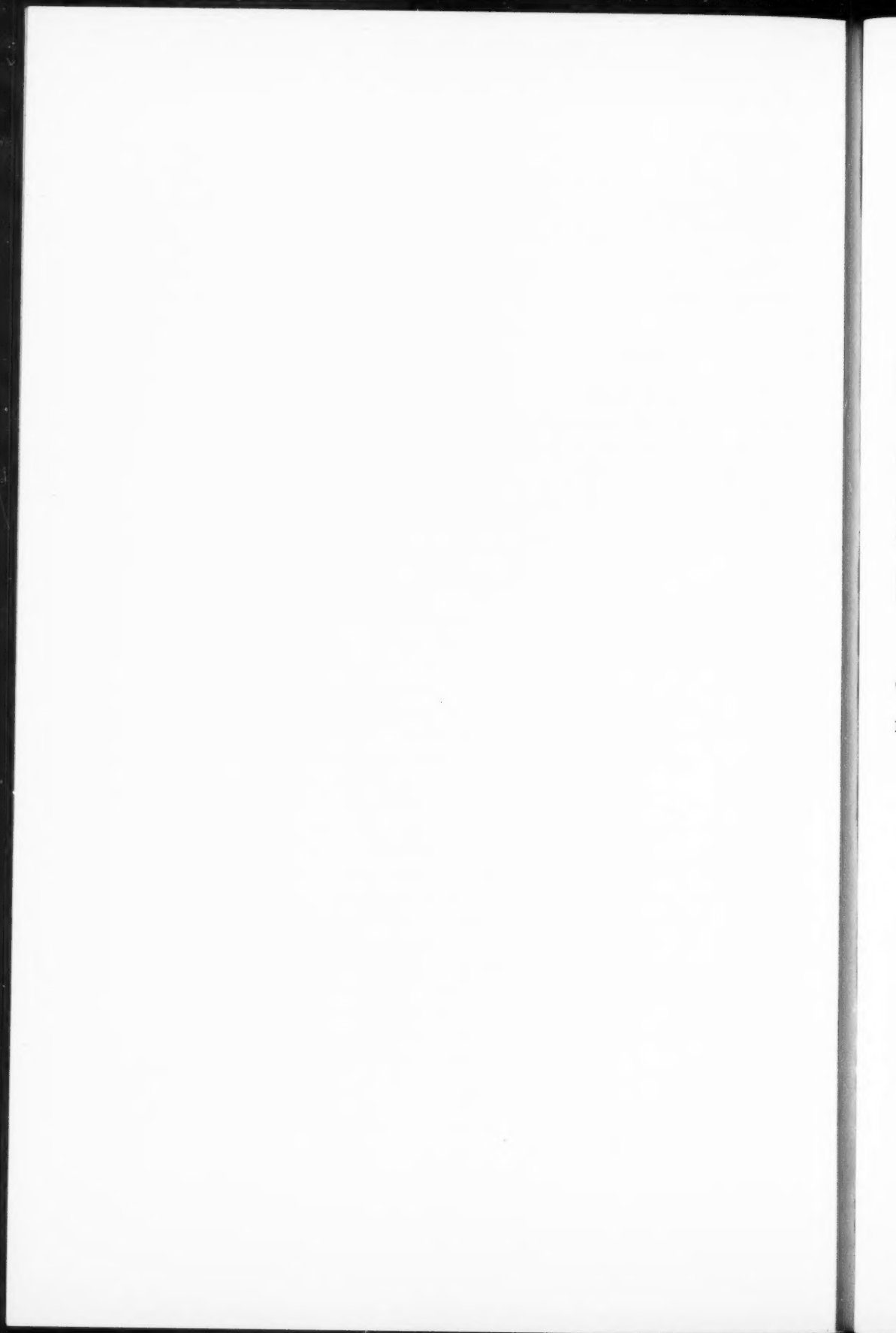
A complete, differential lipid analysis was performed by oxidative micro-methods on the blood plasma of 35 cases provisionally diagnosed as mild

hypothyroidism. Sixteen of these cases responded to thyroid and these all showed a significant lipaemia. Nineteen cases failed to respond to thyroid and the lipid values of these cases were within normal limits. It is concluded that the estimation of plasma lipids is a convenient means of differentiating cases of mild hypothyroidism.

This work was aided financially by the Alice F. Richardson Fund of the Kingston General Hospital.

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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1937

THIRTY-FIRST ANNUAL GENERAL MEETING

THE THIRTY-FIRST ANNUAL GENERAL MEETING was held in Edinburgh on Friday and Saturday, April 16 and 17, 1937, in the Music Classroom of the New University. The attendance book for the meeting was signed by 177 members. The proceedings began at 10 a.m.

The President, Professor G. R. Murray, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

The Treasurer presented the Annual Accounts, which showed a balance of £860 6s. 0d. The Treasurer pointed out that the account of the Clarendon Press for the *Quarterly Journal of Medicine* had not yet been paid, but the balance was nevertheless very satisfactory. It was agreed that the sum of £300 on deposit be invested.

Selection of Place of Meeting for 1938. A letter was received from Professor J. A. Nixon on behalf of the local Members, inviting the Association to meet in Bristol at Whitsuntide, 1938. The invitation was cordially accepted.

Election of Officers

President. Sir Robert W. Philip was elected President. On his election he took the Chair, and expressed the thanks of the Association to the retiring President.

Election of Officers, Executive Committee, Honorary Members, Extra-Ordinary Members, and Ordinary Members then followed.

Executive Committee

President. Sir Robert W. Philip.

Treasurer. Dr. H. Letheby Tidy.

Secretary. Professor L. J. Witts.

Members for England:

Dr. Crighton Bramwell.
Professor A. W. M. Ellis.
Dr. A. Feiling.
Dr. F. G. Hobson.
Dr. H. J. Starling.
Dr. A. W. Stott.

Members for Scotland:

Dr. G. A. Allan.
Dr. W. E. Foggie.
Dr. A. Goodall.

Members for Ireland:

Dr. E. T. Freeman.
Dr. R. Marshall.
Dr. S. I. Turkington.

Honorary Member :

Professor G. R. Murray (President 1936-37).

Extra-Ordinary Members :

Dr. J. Carslaw.
Dr. A. G. Gullan.
Lord Horder.
Sir T. Houston.
Dr. E. B. Leech.
Professor A. E. Naish.
Sir J. Purves-Stewart.
Dr. R. A. Young.

Ordinary Members :

Derrick Melville Dunlop, M.D., Physician, Royal Infirmary, Edinburgh.
Archibald Gilpin, M.D., Assistant Physician, King's College Hospital.
James Andrew Gunn, M.D., Director, Nuffield Institute of Medical Research, Oxford.
William Porter McArthur, M.D., Commandant and Director of Medical Studies, Royal Army Medical College.
Charles Bruce Perry, M.D., Assistant Physician, Bristol General Hospital.
Maurice Shaw, M.D., Physician, West London Hospital.
Joseph Harry Sheldon, M.D., Physician, Royal Hospital, Wolverhampton.
Howard Hilton Stewart, M.D., Physician, Ulster Hospital for Women and Children.
Joseph Houston Wright, M.D., Assistant Physician, Glasgow Royal Infirmary.

Revision of Rule 19. The Secretary moved that the first two sentences of Rule 19 be amended to read as follows :—

‘The subscription of Ordinary and of Extra-Ordinary Members shall be Forty Shillings a year, which shall entitle them to receive a copy of each issue of the *Quarterly Journal of Medicine*’ for the corresponding year.

Subscriptions shall be payable to the Treasurer on Election and on the First of January in each succeeding year.’

This motion was carried.

SCIENTIFIC BUSINESS

Friday Morning

1. PROFESSOR W. M. MITCHELL, introduced by PROFESSOR L. J. WITTS, spoke on *Rheumatic Disease in the Horse*. The communication was an introduction to a pathological demonstration of specimens illustrating the general nature of rheumatic disease as met with in the horse. Clinical signs of the disease were most commonly detected in the limbs in the form of osteo-arthritis lesions, but certain muscular dystrophies such as shivering, stringhalt and laryngeal paralysis appeared to be allied forms of the disease. A disseminated peripheral nerve degeneration was a constant feature in all types of case.

DR. BUCKLEY stressed the analogy of these veterinary conditions with ankylosing spondylitis in man.

2. DR. C. A. GREEN, introduced by PROFESSOR W. T. RITCHIE, discussed *Some Aetiological Aspects of Acute Rheumatism*. Infection with haemolytic streptococci as a factor in the aetiology of acute rheumatism had been investigated in a series of 150 cases of acute rheumatism. In the lesions of this disease no evidence of tissue invasion by haemolytic streptococci, and little support for their production by toxic action, could be found. That rheumatism may, in many cases, be an allergic manifestation of haemolytic streptococcal infection was supported by the frequent occurrence of antecedent throat infections, persistence in the throat flora of haemolytic streptococci, the majority of which were of Lancefield's Group A type, and the high rising antistreptolysin titres of patients' sera during the illness.

DR. C. E. VAN ROOYEN, who had taken part in the same investigation, reported that his attempts to find a filterable virus in acute rheumatism had been completely negative.

PROFESSOR MACKIE thought that the aetiology of acute rheumatism was still an open question. DR. POULTON had found high antistreptolysin titres in erythema nodosum and rheumatoid arthritis, and PROFESSOR DAVIDSON said their results in Aberdeen agreed with those of DR. GREEN. DR. COOPE described a case of streptococcal infection

and rheumatism in which there was a remarkable response to adrenalin. DR. SCHLESINGER said that he and his co-workers were able to find virus and inclusion bodies in acute rheumatism in man, and lesions closely resembling those of acute rheumatism could be produced by injection of a virus suspension into hens.

3. PROFESSOR HENRY MOORE described an enquiry into *Bundle Branch-Block* carried out in association with Edward Keenan, W. R. O'Farrell, and M. A. Moriarty. The enquiry was undertaken in order to discover whether the lesions causing bundle branch-block in three hearts could be located, and, if so, to obtain evidence whether the new or the old electrocardiographic terminology for bundle branch-block was correct. The genetic and conducting systems of the three hearts were fully examined by serial sections, about 120,000 sections having been cut; the lesions were found in each case. In one case there was (according to the new terminology) right and in one left bundle branch-block; and in the other there was at first left bundle branch-block and later this became an indeterminate type of intraventricular block. The results were in favour of the correctness of the new terminology.

DR. WILLIAM EVANS said that right bundle branch-block was commoner than was suggested by the incidence of the electrocardiogram at present attributed to it; he showed another curve which was much more often associated with this lesion.

4. DRS. JOHN PARKINSON, D. EVAN BEDFORD, and W. A. R. THOMSON (introduced) discussed *The Diagnosis of Cardiac Aneurysm*. The clinical, electrocardiographic, and radiological findings in 14 cases of cardiac aneurysm, 5 with necropsy, were summarized. Previous coronary thrombosis, enlargement of the heart, low blood pressure, and a T₁ type of electrocardiogram were common features. Radiograms taken in the anterior and oblique positions showed characteristic deformity of the ventricular contour, and, in 2 cases, calcification of the aneurysm.

DR. DONALD HALL illustrated the improvement in diagnosis by saying that cardiac aneurysm was a pathological curiosity in the days when he wrote his M.D. thesis on this subject.

5. DR. ADOLPHE ABRAHAMS discussed *The Value of Tests for Physical Fitness and Athletic Efficiency*. Physical fitness and athletic efficiency were by no means the same thing. Physical fitness, which might be defined as perfect adaptation to one's environment, comprised a number of factors, some outside the possibility of estimation: athletic efficiency was to some extent directly measurable. The influence of exercise upon the blood pressure and cardiac rate with reference to the 40 millimetre test was reviewed; rapidity of completion of deceleration was considered to be the most satisfactory indication of athletic efficiency and of condition of training; a bad result encouraged a search after a toxin, and examples of such an association were given. In conclusion the importance of co-ordination of all the factors concerned rather than concentration on any individual feature was explained in regard to the super-athlete.

6. DR. JOHN McMICAEL, introduced by PROFESSOR W. T. RITCHIE, discussed *The Output and Response of the Heart in Heart Failure*. In normal persons there occurs a 30 to 40 per cent increase in the output of the heart on changing from the erect to the flat position. This is probably due to an increase of pressure in the veins near the right auricle. In subjects suffering from a moderate degree of heart failure this response of the heart is absent. Following the grouping of cardiac cases suggested by the American Heart Association, there is little change from the normal in Group 1. In Group 2a the output of the heart is lowered in both the erect and reclining positions, and the degree of change which occurs with change of posture is smaller than in the normal healthy individual. In Group 2b the response to change of posture has completely disappeared but the output of the heart is set at a slightly higher level than in Group 2a; it is at this stage that the venous pressure begins to rise. In Group 3 the output of the heart falls to half the normal resting level, or less, and the response to postural change remains absent. These findings can be correlated with observations made on fatigued and poisoned animal hearts.

2 p.m. to 3 p.m.

Clinical Cases in the Royal Infirmary and Demonstrations in the New University and the Royal (Dick) Veterinary College.

3 p.m. *Afternoon Session*

1. DR. ALEXANDER GOODALL gave a communication on the *Treatment of Pneumonia by Intravenous Injection of Iodine*. Ten cubic centimetres of 0.4 per cent solution of

colossal iodine were injected every four hours provided the patient were awake. In practice the iodine was generally administered four times in 24 hours. A striking and constant result was an immediate lowering of the temperature by lysis. Fever usually terminated by the seventh day. Patients were much more easily nursed and mortality had been diminished. Although no proof could be given, some cases appeared to have been aborted. The communication was based on 110 consecutive cases and 50 illustrative temperature charts were shown.

2. DR. C. H. STUART-HARRIS, introduced by PROFESSOR F. R. FRASER, described *The Influenza Epidemic of 1936-37*. The epidemic of influenza during the winter 1936-37 afforded an opportunity for correlating the clinical and pathological features of the epidemic disease due to the ferret-pathogenic virus. In the Services, where the clinical investigation was carried out, the incidence was generally low and did not exceed 15 per cent, and the mortality was very low. Clinically, the typical picture was a 3- or 4-day fever of sudden onset with constitutional rather than local symptoms. The four most important symptoms were malaise, headache, anorexia, and shivering, while cough and a blocked nose were commoner than sore throat or coryza. There was a contrast in the general clinical picture, the appearance of the fauces and the occurrence of chest signs, between this epidemic from which influenza virus was isolated and other epidemics of catarrhal 'tracheitis' which failed to yield the virus.

3. DR. J. G. SCADDING, introduced by PROFESSOR F. R. FRASER, described the *Lung Changes in Influenza*. In a series of 58 cases from 4 of which the influenza virus was isolated, changes classified as 'bronchitis' occurred in 21, and as 'definite consolidation' in 19. Peculiar clinical features observed in these groups were briefly described. Bacteriological study of the sputa showed an increasing predominance of pneumococci as the lung lesion approached more nearly to the common type of pneumonic consolidation. A case of fulminating pneumonia, in whose lung both the influenza virus and *Staphylococcus aureus* were present, was described. The variety of the lung changes was attributed to the varying extent of virus damage and virulence of subsequent bacterial infection.

PROFESSOR FRASER commented on the similarity of these epidemic cases of influenza, but PROFESSOR ELLIS thought that while the present cases were similar to those of May 1918, the cases in the autumn of 1918 were much more severe. DR. TIDY suggested that there were two types of influenza, the pure virus infection, and virus plus secondary invader. DRS. GASKELL and PATRICK stressed the importance of concomitant bacterial infection, and PROFESSOR RYLE and DR. C. H. MILLER spoke of variations in type and degree of influenzal infections, which could not yet be adequately explained.

4. DR. A. JOE compared *The Protective Values of Convalescent Measles Serum and Placental Extract* in 10 ward outbreaks of measles. Of 42 susceptibles receiving convalescent measles serum 7 developed modified measles, and of 40 receiving placental extract 7 showed modified and 5 mild measles. The conclusion was that, while less potent than convalescent serum, placental extract was probably as useful as adult serum.

DRS. PATRICK and PLATT both thought that we should be careful in drawing conclusions from experiments of this kind owing to the variations in infective power of measles. DR. MCSWEENEY had used placental extract with apparent benefit in the treatment of chicken pox.

5. DR. A. P. THOMSON described *Three Cases of Illness Associated with High Eosinophilia*. In one patient histological changes had been found resembling those of tularaemia; no positive agglutinations had been obtained; they were believed to be examples of an unusual type of brucella infection contracted while shooting in South Western Ireland, possibly from cats.

PROFESSOR FRASER thought that eosinophilia of this degree was unusual in tularaemia. DR. TIDY commented on the causes of eosinophilia. DR. HIMSWORTH had seen a similar case in man, while DR. NEWMAN had seen comparable pathological changes in an epidemic amongst turkeys in this country.

6. DR. R. A. HICKLING described two cases of *Splenic and Pulmonary Tuberculosis*. It was emphasized that massive tuberculosis of the spleen never occurred without tuberculous lesions in other organs, and that the diagnosis depended upon the recognition of tuberculous lesions elsewhere in a patient with splenomegaly. Two cases of massive tuberculosis of the spleen were described, in which radiological signs of extensive pulmonary tuberculosis were present. In both cases the radiological evidence of pulmonary tuberculosis disappeared following removal of the spleen, without sanatorium or other treatment, and the patients were well five years and two years, respectively,

after splenectomy. It was suggested that the lungs should be investigated radiologically in all cases of splenomegaly of unknown origin, and that this would occasionally enable the diagnosis of massive tuberculosis of the spleen to be made.

PROFESSOR MURRAY pointed out that massive tuberculosis of the spleen was quite common in the pig. DR. PARKES WEBER emphasized that miliary tuberculosis was often eminently curable.

Annual Dinner

The annual dinner was held at the Royal College of Physicians of Edinburgh. The President, Sir Robert W. Philip, was in the Chair. The official guests included the Sheriff of the Lothians and Peebles-shire; the Lord Rector of the University; the President of the Royal College of Surgeons of Edinburgh; the Dean of the Thistle and Chapel Royal; the Chairman of the Royal Infirmary Board of Managers. There were present 138 members and guests.

Saturday, 10 a.m., Morning Session

1. PROFESSOR L. S. P. DAVIDSON gave data regarding *Certain Rare Forms of Severe Macrocytic Anaemia*. The series comprised two cases of microcytic hypochromic anaemia which developed macrocytic anaemia; three cases of acquired acholuric jaundice, one with cirrhosis of the liver in addition; two cases of cirrhosis of the liver; one case of aleukaemic leukaemia; one case of reticulo-endotheliosis; one case of ? achrestic ? aplastic anaemia.

PROFESSOR WITTS described a series of macrocytic anaemias of which 2 were due to cirrhosis hepatis and 8 were of the aplastic-achrestic type. DR. PARKES WEBER thought that certain severe anaemias still remained obscure, and PROFESSOR MCNEE thought it was premature to embark on their classification until we knew more about the physiology of haemopoiesis.

2. DR. W. RITCHIE RUSSELL described *Some Observations on Vitamin B₁ Therapy*. In cases of possible vitamin B₁ deficiency, the vitamin should be given by injection, as absorption from the alimentary canal might be defective. Several forms of polyneuritis responded well to the administration of this vitamin, including the polyneuritis of pernicious anaemia.

3. DR. C. C. UNGLEY reported *Observations on Polyneuritis, with Special Reference to Vitamin B₁ Deficiency*. Of 15 cases of polyneuritis 7 appeared to be primarily 'nutritional', due to dietary deficiency and gastro-intestinal abnormalities. In this group nutritional changes in blood, bones, tongue, etc., were common, sensory disturbances marked and cerebrospinal fluid protein normal. Urinary excretion of vitamin B₁ was deficient in these and also in some of the non-nutritional group; vitamin B₁ in blood was sometimes normal even when excretion was poor. The effect of vitamin B₁ injections (500 to 1,000 I.U. daily) was often slow and difficult to assess. The role of vitamin B₁ was not clear-cut: associated deficiencies (e.g. A or B₂ complex) might play a part in the aetiology of nutritional polyneuritis.

PROFESSOR RYLE was impressed by the frequency of conditioned deficiencies in alimentary diseases and DR. HURST doubted whether vitamin B deficiency ever developed in this country in the absence of a gastro-intestinal lesion. DR. ANDERSON said that nutritional polyneuritis should be distinguished from infectious polyneuritis, in which the protein of the spinal fluid was much increased. DR. MANSON-BAHR pointed out that we always came back to tropical medicine.

4. DR. IVOR J. DAVIES reported *Some Uncommon Sequelae of Encephalitis Lethargica*. One case of Parkinsonism, showing the ordinary features with an occasional oculo-gyric crisis, and bed-ridden for the last three years of his life, was occasionally subject to what might be termed 'congestive seizures'. In these attacks he became febrile to 102° or 103° with profuse sweating and intense flushing. There was marked restlessness with increased tremor. Such attacks would last on an average about 8 hours and a few only of these attacks coincided with the oculo-gyric crisis. There was no source of sepsis. Another case of Parkinsonism was complicated by abdominal attacks closely resembling acute paralytic ileus. Marked abdominal distension with collapse of the bases of the lungs and cardiac embarrassment occurred suddenly without apparent cause. The attacks were infrequent and were only relieved by repeated doses of calomel and the passage of a rectal tube with restorative measures. Death ultimately occurred in one of these attacks.

PROFESSOR A. J. HALL gave a luminous description of the slowing of the human machine in Parkinsonism and its speeding-up by certain exogenous and endogenous influences.

5. DR. GEORGE GRAHAM and W. G. OAKLEY (introduced) discussed *The Treatment of Renal Rickets*. The prognosis of renal rickets was bad as regarded both the duration of life and the changes in the bones. The authors had confirmed the observation that the alkali reserve was low in these cases. They had found that when a daily dose of alkali was given, which was sufficient to keep the alkali reserve normal, the retention of the urea in the blood got less. They had given 6,000 units of vitamin D at the same time and had observed complete healing of the bones in one case in three years and great improvement in nine months in a second case.

DR. MORRIS confirmed the good results of alkali, which should nevertheless be administered with caution because the acid-base equilibrium was unstable; calcium also might help the kidney. DR. IZOD BENNETT thought it was the sodium ion which benefited renal function. DR. PLATT also confirmed the values of alkali, but pointed out that excess might induce oedema. DR. BARBER agreed that spontaneous oedema never appeared in these cases. DR. POULTON warned members that very high doses of vitamin D damaged the kidney.

6. DRS. F. PARKES WEBER and A. W. STOTT, with STANFORD CADE and R. J. V. PULVERTAFT (introduced) described *Systematized Atypical Amyloidosis with Macroglossia (the Lubarsch-Pick Syndrome)*. Amyloidosis might be atypical in the distribution of the deposits; in the staining reactions of the deposits; and in the absence of any recognized cause. Systematized atypical amyloidosis with enlargement of the tongue constituted a definite, though rare, clinical and pathological syndrome, which might be termed the Lubarsch-Pick Syndrome, from the pathologists who specially drew attention to its existence. As yet eleven examples of this syndrome had been described, of which the present one, in a woman, aged 48 years, had been diagnosed during life from the microscopic examination of the tongue, part of which was removed on account of its enlargement, and from biopsies on the pad of a finger and on a piece of gastrocnemius muscle. Though the exact cause was unknown, the syndrome was apparently due to a metabolic disturbance of some kind, and it was noteworthy that a kind of atypical amyloidosis might occur in association with myelomatosis (multiple myeloma). The relatively frequent association of two such rare syndromes could hardly be a mere coincidence.

2 p.m. to 3 p.m.

Clinical Cases in the Royal Infirmary and Demonstrations in the New University and the Royal (Dick) Veterinary College.

3 p.m. Afternoon Session

1. DR. A. R. PARSONS described a case of *Diabetic Coma without Ketosis* in a woman of 70, who was admitted to hospital profoundly unconscious. The urine contained abundant sugar and a faint trace of albumin but no acetone or diacetic acid. The blood sugar was 378 mg. per cent. The knee jerks were not elicited. The patient died about 18 hours later. Autopsy revealed slight cirrhosis of the liver with some fatty infiltration; the pancreatic islets appeared normal, but the cells all had rounded nuclei and very small bodies. There was much necrosis of tubular epithelium and apparent fatty degeneration in the kidneys. There were some hyaline arteriosclerotic glomeruli and increase of fibrous tissue in places. There was no acetone in the cerebrospinal fluid and attempts to distil acetone from the blood failed.

An interesting discussion followed from which it appeared that cases of this kind were not unusual though their explanation was obscure. It was emphasized that even though coma occurred in a known diabetic, it could not be assumed that it was true diabetic coma. DR. MORRIS thought that the attacks were often cerebral. DR. HIMSWORTH had seen two cases, one due to bilateral haemorrhage and the other to acute atrophy of the suprarenal glands. DRS. GRAHAM, POULTON, and OLIVER also described cases of diabetic coma without ketosis.

2. DR. NOAH MORRIS described the use of *Protamine Insulin in the Treatment of Diabetic Children*. The advantages of protamine insulin in the treatment of diabetes mellitus in childhood were (1) the smaller number of injections, (2) the greater spread-over of carbohydrate food, (3) the absence of uncontrolled periods and (4) the much greater feeling of well-being and energy. An inadequate dose did not show the prolonged

action so that when patients were transferred from ordinary to protamine insulin it was advisable to begin with the same number of units and then reduce as morning glycosuria disappeared. Hypoglycaemic reactions occurred at any time but had been most frequent about mid-day and 6 p.m.; usually warning symptoms had permitted preventive measures being adopted. Incidental glycosuria during the day was resistant, especially in old patients, but often tended to disappear when the morning urine had been free of sugar for some weeks.

3. DR. T. IZOD BENNETT discussing his *Experiences and Experiments with the New Insulins* said that the observations of himself and his assistants at the Middlesex Hospital agreed in many ways with those which DR. NOAH MORRIS had just reported in children; he could not, however, agree that the action of zinc insulin was parallel to that of Hagedorn's protamine insulin. The action of zinc insulin, whether in the form marketed by the English manufacturers or in the form of the so-called crystalline insulin, was much slower and more prolonged. His observations on normal men showed that these insulins reached their climax at 12 to 14 hours after administration. The new insulins were of great potential value and permitted us to keep many cases stabilized on a single daily injection. It was necessary, however, to utter a very serious warning against their indiscriminate use as they carried the risk of prolonged and most severe hypoglycaemia; it was to be feared that this, the first year of their trial, would be marked by deaths which could only be prevented if the profession as a whole realized the danger as well as the value of the new weapons.

DR. H. P. HIMSWORTH (introduced) compared the action of protamine insulin and zinc protamine insulin. Under conditions in which ordinary insulin exerted its maximum effect in 2 to 3 hours and was spent at the end of 6 hours, protamine insulin produced its maximum effect in 6 to 10 hours and had worn off by 12 to 18 hours, while zinc protamine insulin showed its greatest effect in 8 to 15 hours and was still acting 20 to 30 hours later. The slowness with which these new insulins came into action made them ineffective in suppressing alimentary hyperglycaemia and rendered necessary the giving of auxiliary injections of quick acting insulin. With protamine insulin, ordinary insulin was an effective auxiliary; with zinc protamine insulin, protamine insulin was more effective. Attention was drawn to the danger of severe hypoglycaemic reaction from zinc protamine insulin.

DR. A. P. THOMSON thought that the new insulins were perfectly safe so long as the dosage was moderate. DR. OLIVER thought there was risk of diabetic coma developing during infection in diabetics who were using these slowly acting insulins.

4. DR. E. BULMER spoke on *Terminal Ileitis*. After briefly summarizing the literature and clinical features, he gave details of a patient. She had had recurrent abdominal pain for 11 years, and during the last year intermittent intestinal obstruction with loss of weight. A barium enema showed a deformed terminal ileum. At operation the terminal ileum was removed; it showed changes characteristic of the stenotic type of ileitis. Both the specimen and microscopic slides were demonstrated.

5. DR. GEOFFREY EVANS reported three cases of *Regional Ileitis*, and showed museum specimens of two of them. From his experience of one patient in whom the disease was at an early stage (the lesion showing ulceration and oedema with relatively little small-cell infiltration and no fibrosis), DR. EVANS suggested that healing might occur by resolution, and without fibrosis and cicatrization. He also remarked that in two of his cases a lateral anastomosis of the ileum had been successfully performed by MR. HAROLD WILSON.

6. DR. A. F. HURST described a case of *Regional Colitis* in a patient presenting all the usual symptoms of severe ulcerative colitis but a normal appearance of the mucous membrane on sigmoidoscopy. X-Rays revealed polypoid colitis localised to the descending colon. The affected part was removed with complete recovery. *B. Asiaticus*, which was agglutinated by the patient's serum up to 1 in 200, was isolated in large numbers from the stools and excised part of the colon, but not the transverse colon, and disappeared completely from the stools immediately after the operation.

DR. MANSON-BAHR spoke slightly of the pathogenic powers of *B. Asiaticus*, which was not so sinister an organism as its name suggested. PROFESSOR DAVIDSON had treated three cases of Crohn's disease during the last twelve months. DR. DAVID SMITH had had three cases, of which one followed dysentery and another pulmonary tuberculosis.

At the conclusion of the meeting SIR WALTER LANGDON BROWN proposed a hearty vote of thanks to the Edinburgh members for their hospitality, congratulating them on

the success of the meeting and mentioning especially the services of the President, Sir Robert W. Philip; the Local Secretary, Dr. J. D. Comrie; and the Dinner Secretary, Dr. J. K. Slater. This was carried with acclamation.

General appreciation was expressed on the substance of the communications, but there were again complaints at the manner of presentation of some of them. It is therefore hoped that the Secretary may be permitted, without seeming to give offence, to summarize the advice given to him for the guidance of speakers at future meetings. The Music Classroom was not an easy room to speak in, but some of the speakers might have surmounted the difficulties more creditably. Diagrams which are too complex or which follow one another in a rapid sequence serve to confuse rather than to enlighten an audience, and members are advised to follow the technique of the comic strip rather than the documentary film. Supplementary communications should be brief or they exhaust the time available for discussion. Rule XVI states that communications shall be spoken and not read, and that no such communication shall last longer than 15 minutes. No nicer compliment can be paid to the Association than to rehearse a communication thoroughly and to eschew the sins of inaudibility, obscurity, and tediousness.

B.C.
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